

# **Medicaid Dossier for *Avandamet***

This response may include reference to information about Avandia® (rosiglitazone maleate) Tablets; and Avandamet® (rosiglitazone maleate and metformin hydrochloride) Tablets.

**Some information contained in this response may not be included in the approved Prescribing Information. This response is not intended to offer recommendations for administering this product in a manner inconsistent with its approved labeling.**

**In order for GlaxoSmithKline to monitor the safety of our products, we encourage healthcare professionals to report adverse events or suspected overdoses to the company at 888-825-5249. Please consult the attached Prescribing Information.**

**This response was developed according to the principles of evidence-based medicine and, therefore, references may not be all-inclusive.**

## TABLE OF CONTENTS

<b>1. CHANGE SUMMARY . . . . .</b>	<b>7</b>
<b>2. PRODUCT SUMMARY . . . . .</b>	<b>8</b>
<b>3. DISEASE DESCRIPTION. . . . .</b>	<b>10</b>
<b>4. PRODUCT DESCRIPTION . . . . .</b>	<b>15</b>
<b>4.1 Generic Name, Brand Name and Therapeutic Class . . . . .</b>	<b>15</b>
<b>4.2 Dosage Forms, Package Sizes, and NDC for All Formulations . . . . .</b>	<b>15</b>
<b>4.3 AWP and WAC Cost per Unit . . . . .</b>	<b>16</b>
<b>4.4 AHFS or Other Drug Classification . . . . .</b>	<b>16</b>
<b>4.5 FDA Approved Indications . . . . .</b>	<b>16</b>
<b>4.6 Pharmacology . . . . .</b>	<b>16</b>
<b>4.7 Pharmacokinetics/Pharmacodynamics . . . . .</b>	<b>16</b>
<b>4.8 Contraindications . . . . .</b>	<b>16</b>
<b>4.9 Warnings/Precautions . . . . .</b>	<b>16</b>
<b>4.10 Adverse Events . . . . .</b>	<b>17</b>
<b>4.11 Other Clinical Considerations . . . . .</b>	<b>28</b>
<b>4.12 Drug/Food/Disease Interactions . . . . .</b>	<b>28</b>
<b>4.13 Dosing and Administration . . . . .</b>	<b>28</b>
<b>4.14 Co-prescribed/Concomitant Therapies . . . . .</b>	<b>28</b>
<b>5. EFFICACY AND SAFETY TRIALS (FDA APPROVED) . . . . .</b>	<b>29</b>
<b>5.1 Efficacy and Safety of Avandia Add-on Therapy with Metformin in Type 2 Diabetes . . . . .</b>	<b>29</b>
<b>5.2 Use of Avandamet as Initial Therapy for the Treatment of Type 2 Diabetes . . . . .</b>	<b>32</b>
<b>6. ADDITIONAL SAFETY INFORMATION . . . . .</b>	<b>35</b>
<b>6.1 Interim Analysis of the RECORD Study . . . . .</b>	<b>35</b>
<b>7. COMPARATIVE DATA . . . . .</b>	<b>36</b>
<b>7.1 Results of the ADOPT Trial . . . . .</b>	<b>36</b>
<b>7.2 The Risk of Myocardial Ischemic Events with Avandia Compared to Actos . . . . .</b>	<b>40</b>
<b>8. OTHER STUDIED USES. . . . .</b>	<b>48</b>
<b>8.1 Avandamet and Polycystic Ovary Syndrome (PCOS) . . . . .</b>	<b>48</b>
<b>8.2 Effect of Avandamet on Lipids in Drug-Naïve Patients with Type 2 Diabetes . . . . .</b>	<b>49</b>
<b>9. OUTCOME AND ECONOMIC EVALUATION . . . . .</b>	<b>50</b>
<b>10. ECONOMIC MODEL . . . . .</b>	<b>51</b>
<b>11. REFERENCES . . . . .</b>	<b>54</b>

## **List of Figures**

<b>Figure 1. Forest Plot of Odds Ratios (95% Confidence Intervals) for Myocardial Ischemic Events in the Meta-Analysis of 42 Clinical Trials. . . . .</b>	<b>18</b>
<b>Figure 2. Hazard Ratios for the Risk of MACE (Myocardial Infarction, Cardiovascular Death, or Stroke), Myocardial Infarction, and Total Mortality With Avandia Compared With a Control Group . . . . .</b>	<b>19</b>
<b>Figure 3. Mean Change in Body Weight at 24 Weeks . . . . .</b>	<b>22</b>

## List of Tables

<b>Table 1. Therapeutic Options for the Treatment of Type 2 Diabetes . . . . .</b>	<b>12</b>
<b>Table 2. GI Adverse Events During Pre-approval Combination Trials with <i>Avandia</i> and Metformin * . . . . .</b>	<b>20</b>
<b>Table 3. Mean Change from Baseline to Week 24 in the DHSI*. . . . .</b>	<b>21</b>
<b>Table 4. On-therapy Gastrointestinal Adverse Events Reported by <math>\geq 10\%</math> of Patients . . . . .</b>	<b>21</b>
<b>Table 5. Weight Changes (kg) from Baseline During Clinical Trials with <i>Avandia</i> in Combination with Metformin. . . . .</b>	<b>22</b>
<b>Table 6. Incidence of Edema with <i>Avandia</i> in Controlled Clinical Trials of Type 2 Diabetes Patients . . . . .</b>	<b>23</b>
<b>Table 7. Emergent Cardiovascular Adverse Events (Study 211) . . . . .</b>	<b>24</b>
<b>Table 8. Fracture Rates Reported in Women by Menopausal Status and Age . . . . .</b>	<b>26</b>
<b>Table 9. Patients with Fractures in ADOPT. . . . .</b>	<b>27</b>
<b>Table 10. Evaluation of <i>Avandia</i> in Combination with Metformin - Pivotal Clinical Studies . . . . .</b>	<b>29</b>
<b>Table 11. Adverse Events Reported During the Pivotal Clinical Studies of <i>Avandia</i> in Combination with Metformin* . . . . .</b>	<b>30</b>
<b>Table 12. Glycemic Results in Mexican Patients at 26 weeks . . . . .</b>	<b>31</b>
<b>Table 13. Change in HbA1c and FPG * . . . . .</b>	<b>32</b>
<b>Table 14. Change in HbA1c and FPG from Baseline to Week 32 in Study 007 (ITT with LOCF) . . . . .</b>	<b>33</b>
<b>Table 15. On-Therapy Adverse Events Reported by <math>\geq 5\%</math> of Subjects in Study 007 (Safety Population) . . . . .</b>	<b>34</b>
<b>Table 16. Hazard Ratios for the Risk of MACE, Myocardial Infarction, and Total Mortality . . . . .</b>	<b>36</b>
<b>Table 17. Ischemic Cardiovascular Events in ADOPT . . . . .</b>	<b>39</b>
<b>Table 18. Hazard Ratio of Composite and Individual Outcomes: <i>Avandia</i> regimens vs. Pioglitazone regimens . . . . .</b>	<b>41</b>
<b>Table 19. Adjusted Hazard Ratios of Acute MI including and Excluding Unstable Angina for <i>Avandia</i>, Pioglitazone and Other OADs . . . . .</b>	<b>43</b>
<b>Table 20. Adjusted Hazards Ratios of Acute MI including and Excluding Unstable Angina in Monotherapy Cohorts for <i>Avandia</i>, Pioglitazone, and Other Oral Antidiabetic Agents. . . . .</b>	<b>43</b>
<b>Table 21. Adjusted HR of Acute MI Including and Excluding Unstable Angina for <i>Avandia</i>, Pioglitazone, and Other Oral Antidiabetic Agents Limited to Treatment Period . . . . .</b>	<b>43</b>
<b>Table 22. Annual Incidence Rates of Acute Myocardial Infarction Averaged Over the 4 Year Period in TRICARE Prime (2003-2006) . . . . .</b>	<b>44</b>
<b>Table 23. Rate Ratios of Acute Myocardial Infarction and All-Cause Mortality With the Use of Thiazolidinediones Compared to Other Oral Hypoglycemic Agent Combination Therapies . . . . .</b>	<b>46</b>

<b>Table 24. Percent Change from Baseline to Week 32 in Lipid Parameters* (Safety Population)</b>	50
<b>Table 25. Percentage of Patients on Each Product (hypothetical distribution)</b>	52
<b>Table 26. Average Cost Per Day of Therapies of Interest</b>	53
<b>Table 27. Patients Not Controlled with Metformin Monotherapy - Estimated Total Economic Impact</b>	53

## 1. Change Summary

The purpose of the Change Summary is to provide a description of the significant changes/revisions to the dossier from the previous version(s). The following indicates sections within the dossier that where new clinical data has been added to the dossier within the past year:

- Section 2 Product Summary
- Section 4.9 Warnings/Precautions
- Section 4.10 Adverse Events:
  - The Risk of Myocardial Ischemic Events in Patients Treated with *Avandia*
  - *Avandia* and Fractures
  - Reports of Macular Edema with *Avandia*
- Section 6 Comparative Data:
  - 6.1 Results of the ADOPT Trial
  - 6.2 Risk of Myocardial Ischemic Events with *Avandia* Compared to Actos

## 2. PRODUCT SUMMARY

### About Type 2 diabetes

- Over 23 million people in the United States have diabetes. Type 2 diabetes accounts for 90-95% of all diagnosed cases. <sup>(1)</sup>
- Type 2 diabetes is considered one of the most costly diseases in the United States, in part due to its association with microvascular and macrovascular complications.<sup>(2)</sup>
- Approximately 90% of patients with type 2 diabetes are insulin resistant.<sup>(3,4)</sup>
- Currently, there are six main classes of oral antidiabetic medications.<sup>(5)</sup> The thiazolidinedione (TZD) class of agents targets a core underlying defect of type 2 diabetes, insulin resistance.<sup>(3)</sup>
- Type 2 diabetes is characterized by a progressive loss of glycemic control marked by an increase in insulin resistance and decline in beta-cell function.<sup>(6,7)</sup>

### About *Avandamet*

- *Avandamet* is a fixed-dose combination tablet, which contains two oral antihyperglycemic drugs used in the management of type 2 diabetes providing complimentary mechanisms of action: a thiazolidinedione (rosiglitazone maleate) and a biguanide (metformin HCl).<sup>(8)</sup>
- *Avandamet* is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus when treatment with dual rosiglitazone and metformin therapy is appropriate.<sup>(8)</sup>
- In a 32-week, double-blind study (Study 007), 468 drug-naïve patients with type 2 diabetes mellitus inadequately controlled with diet and exercise alone were randomized to *Avandamet*, rosiglitazone, or metformin as initial therapy.<sup>(8,9)</sup> Significant improvements in fasting plasma glucose (FPG) and HbA1c were observed in patients treated with *Avandamet* compared to either rosiglitazone or metformin alone. The proportion of subjects [intent to treat (ITT) with Last Observation Carried Forward] with HbA1c <7% was higher in subjects that received *Avandamet* (77%) compared to those who received metformin (57%) and rosiglitazone (58%) monotherapies at Week 32.
- Patients screened in the double-blind clinical trial described above with HbA1c >11% or FPG >270 mg/dL were not eligible for blinded treatment but were treated with open-label *Avandamet* (4 mg/1,000 mg up to a maximum dose of 8 mg/2,000 mg) for 24 weeks (Study 004).<sup>(8,10)</sup> Treatment with *Avandamet* reduced mean HbA1c from a baseline of 11.8% to 7.8% and mean FPG from a baseline of 305 mg/dL to 166 mg/dL.
- Adding *Avandia* to metformin helped patients reach HbA1c goal.<sup>(8) (11)</sup>
  - In two 26-week, double-blind trials, *Avandia* in combination with metformin significantly reduced HbA1c and FPG levels compared to metformin alone.<sup>(8)</sup>
  - A 24-week, double-blind study (Study 284) demonstrated that a greater percentage of patients receiving *Avandia* in combination with submaximal doses of metformin (1000 mg/day) reached an HbA1c of < 7% compared to the uptitrated metformin monotherapy group (2000 mg/day) [58%, (172/296) vs. 48%, (134/277), respectively]. <sup>(11)</sup>
    - Additionally, 41% (121/296) of patients in the combination group were able to achieve the American Association of Clinical Endocrinologists (AACE) HbA1c goal of ≤ 6.5% compared to 28% (78/277) in the uptitrated metformin alone group.
- *In vitro* drug metabolism studies suggest that rosiglitazone does not inhibit any of the major P450 enzymes at clinically relevant concentrations. Changes in diabetes treatment may be needed based upon clinical response when an inhibitor (such as gemfibrozil) or inducer (such as rifampin) of CYP2C8 is initiated or discontinued during rosiglitazone treatment.<sup>(8)</sup> In several pharmacokinetic and/or pharmacodynamic studies, rosiglitazone had no clinically significant drug interactions reported with a variety of medications including acarbose, digoxin, ethanol, glimepiride, metformin, nifedipine, oral contraceptives, ranitidine, sucralfate, and warfarin.<sup>(8,12,13,14,15,16,17,18,19)</sup> Metformin has been studied concomitantly with nifedipine, furosemide, propranolol, ibuprofen and rosiglitazone, and appears to be associated with few significant drug interactions. However, there is a potential for a drug interaction between metformin and drugs that are excreted by the proximal



renal tubules (i.e., cimetidine). Please refer to the Prescribing Information for *Avandamet* for additional drug interactions.<sup>(8)</sup>

### Pharmacoeconomic data

- A retrospective pharmacy claims analysis from the database of a large health benefits company identified members with at least one pharmacy claim for rosiglitazone or metformin during the identification period and who were continuously enrolled in the health plan and maintained continuous medication therapy during the study period. <sup>(20)</sup> *Avandamet* was shown to improve patient adherence to therapy compared to patients who remained on separate tablets. Medication possession ratio (MRP) was used to measure medication adherence. Patients switching from either monotherapy to *Avandamet* had significantly less reduction in the mean MRP change than those switching from either monotherapy to dual therapy (-4.6% vs. -12.4%,  $P < 0.001$ ). Further, the analysis revealed that patients switching from dual therapy to *Avandamet* also exhibited a significant improvement in the mean MRP change compared to those on continuous dual therapy (3.5% vs. -1.3%,  $P < 0.005$ ).

### Important Clinical Considerations When prescribing AVANDIA® (rosiglitazone maleate), AVANDAMET® (rosiglitazone maleate/metformin HCl) and AVANDARYL® (rosiglitazone maleate and glimepiride)

*Avandia* is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type diabetes.

*Avandamet* is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus when treatment with dual rosiglitazone and metformin therapy is appropriate.

*Avandaryl* is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus when treatment with dual rosiglitazone and glimepiride therapy is appropriate.

### Important Limitations of Use for *Avandia*, *Avandamet*, and *Avandaryl*

- Coadministration of rosiglitazone and insulin is not recommended
- Use of rosiglitazone with nitrates is not recommended

### CONTRAINDICATION FOR *AVANDIA*, *avandamet*, and *avandaryl*:

- Initiation of rosiglitazone in patients with established New York Heart Association (NYHA) Class III or IV heart failure

### Additional CONTRAINDICATIONS FOR *AVANDAMET*:

- Renal disease or renal dysfunction. Do not initiate in patients  $\geq 80$  years of age unless creatinine clearance is normal. Temporarily discontinue *Avandamet* in patients receiving intravascular iodinated contrast materials. Restart *Avandamet* only after normal renal function has been established
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis. Withhold therapy in the presence of any condition associated with hypoxemia, dehydration, or sepsis

### Additional CONTRAINDICATION FOR *AVANDARYL*:

- Diabetic ketoacidosis, with or without coma. This condition should be treated with insulin

### Boxed WARNING: For *AVANDIA*, *AVANDAMET* and *AVANDARYL*: CONGESTIVE HEART FAILURE AND MYOCARDIAL ISCHEMIA

- Thiazolidinediones, including rosiglitazone, cause or exacerbate congestive heart failure in some patients. Observe patients carefully for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnea, and/or edema). If these signs and symptoms develop, the heart failure should be managed according to current standards of care. Furthermore, discontinuation or dose reduction of rosiglitazone must be considered
- Rosiglitazone is not recommended in patients with symptomatic heart failure
- A meta-analysis of 42 clinical studies (mean duration 6 months; 14,237 total patients), most of which compared rosiglitazone to placebo, showed rosiglitazone to be associated with an increased

risk of myocardial ischemic events such as angina or myocardial infarction. Three other studies (mean duration 41 months; 14,067 total patients), comparing rosiglitazone to some other approved oral antidiabetic agents or placebo, have not confirmed or excluded this risk. In their entirety, the available data on the risk of myocardial ischemia are inconclusive

#### **For *AVANDAMET*: LACTIC ACIDOSIS**

- **Lactic acidosis is a rare but serious metabolic complication that can occur due to metformin accumulation during therapy with *Avandamet*.** The risk of lactic acidosis increases in patients with renal dysfunction, congestive heart failure requiring pharmacologic management, and in the elderly. The onset of lactic acidosis often is subtle and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. Patients should be cautioned against excessive alcohol intake when taking *Avandamet*. *Avandamet* should be temporarily discontinued prior to surgical procedures, specifically those involving restricted intake of food and fluids. *Avandamet* should generally be avoided in patients with clinical or laboratory evidence of hepatic disease

#### **OTHER WARNINGS AND PRECAUTIONS for *AVANDIA*, *AVANDAMET*, and *AVANDARYL***

- Initiation of *Avandia* is not recommended for patients experiencing an acute coronary event and discontinuation of *Avandia* during this event should be considered
- Dose-related edema, weight gain, and anemia may occur
- Rosiglitazone should not be started in patients with active liver disease or with ALT levels >2.5x the upper limit of normal. Check liver enzymes prior to initiation of rosiglitazone and periodically per clinical judgment
- *Avandia*, in combination with other hypoglycemic agents, may increase the risk of hypoglycemia
- Macular edema has been reported
- Increased incidence of bone fracture in female patients
- Resumption of ovulation can occur

#### ***ADDITIONAL CONSIDERATIONS FOR AVANDARYL:***

- Increased risk of cardiovascular mortality was associated with the sulfonylurea tolbutamide. It is prudent to consider that this warning may apply to all sulfonylureas
- Severe hypoglycemia may occur. Elderly, debilitated, or malnourished patients, or patients with adrenal, pituitary, renal, or hepatic insufficiency may be more sensitive to the glucose-lowering effect of sulfonylureas

### **3. DISEASE DESCRIPTION**

#### ***Epidemiology and Risk Factors***

Over 23 million people (7.8% of the population) in the United States have diabetes.<sup>(21)</sup> Of these, 5.7 million people are not aware that they have the disease. Diabetes was the seventh deadliest disease in the United States in 2006 and is associated with a number of serious microvascular and macrovascular complications.

Type 2 diabetes accounts for 90-95 % of all diagnosed cases of diabetes.<sup>(21)</sup> The major risk factors for developing type 2 diabetes include a family history of diabetes, overweight or obesity, physical inactivity, race/ethnicity, previously identified impaired glucose tolerance or impaired fasting glucose, hypertension, low high-density lipoprotein (HDL) cholesterol or high triglycerides, a history of gestational diabetes mellitus or delivering a baby weighing > 9 pounds, polycystic ovary syndrome, and a history of cardiovascular disease.<sup>(22)</sup>

#### ***Pathophysiology***

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. <sup>(23)</sup> Type 2 diabetes results from insulin resistance (primarily at the liver, skeletal muscle, and adipose tissue), combined with impaired insulin secretion.<sup>(24)</sup> Over 90% of patients with type 2 diabetes are insulin resistant. <sup>(25)</sup> Insulin resistance is often detectable 15 to 20 years before the onset of type 2 diabetes.<sup>(26)</sup> In addition to being associated with type 2 diabetes, insulin

resistance is also believed to be associated with a cluster of metabolic abnormalities that include impaired glucose tolerance, hypertension, abdominal obesity, dyslipidemia, and prothrombotic and proinflammatory states.<sup>(27)</sup> Collectively, these components are known as the metabolic syndrome.

When the peripheral tissues do not adequately respond to insulin, there is decreased peripheral glucose uptake.<sup>(28)</sup> This causes circulating blood glucose concentrations to rise. The resulting hyperglycemia then stimulates the pancreas to augment insulin secretion, leading to hyperinsulinemia. Early in the disease course but before the development of type 2 diabetes, the pancreas is able to overcome insulin resistance and maintain euglycemia. However, as the disease progresses to impaired glucose tolerance and type 2 diabetes, the pancreas is no longer able to provide enough insulin to overcome the body's resistance and hyperglycemia develops.

### ***Clinical Presentation***

Type 2 diabetes is often asymptomatic in its early stages and therefore can remain undiagnosed for many years.<sup>(22)</sup> However, patients experiencing symptoms can present with complaints of frequent urination, unusual thirst, extreme hunger, unusual weight loss, extreme fatigue, irritability, frequent infections, blurred vision, cuts/bruises that are slow to heal, tingling/numbness in the hands or feet, and recurring skin, gum, or bladder infections.<sup>(29)</sup> <sup>(23)</sup> Many patients remain undiagnosed until they present with one of the complications of diabetes. Long-standing hyperglycemia may result in microvascular complications including retinopathy, nephropathy, and neuropathy or macrovascular complications including cardiovascular disease, cerebrovascular disease, and peripheral vascular disease.

Current American Diabetes Association (ADA) recommendations for the diagnosis of type 2 diabetes are available at [www.diabetes.org](http://www.diabetes.org).

### ***Approaches to Treatment-Principle Options/Practice Patterns/Place in Therapy***

The management plan for a patient with diabetes should be individualized based on several patient characteristics including age, eating patterns, physical activity, presence of complications, etc. <sup>(22)</sup> Lifestyle modifications (i.e., diet, exercise, and weight loss) should be the center of any therapeutic program since they have been shown to lower glucose concentrations and may help improve risk factors for microvascular complications and possibly cardiovascular disease. <sup>(30)</sup>

Pharmacologic treatment of type 2 diabetes includes oral antidiabetic medications that focus mainly on increasing insulin secretion, decreasing hepatic glucose production, or reducing insulin resistance. <sup>(30)</sup> A summary of the different classes of oral antidiabetic agents is included in Table 1.

Maintaining glycemic control is a key goal in helping to minimize the complications associated with type 2 diabetes. Currently, glycemic treatment goals recommended by the ADA include an A1c of <7%, preprandial plasma glucose of 70-130 mg/dL, and peak postprandial plasma glucose <180 mg/dL.<sup>(22)</sup> The American Association of Clinical Endocrinologists (AACE) recommends an A1c of ≤ 6.5%, preprandial glucose of ≤ 110 mg/dL, and postprandial glucose ≤ 140 mg/dL.<sup>(31)</sup> Since diabetes is a progressive disease, the majority of patients will often require more than one medication to treat their diabetes. <sup>(32)</sup> <sup>(33)</sup> Data from the United Kingdom Prospective Diabetes Study (UKPDS) found that the proportion of patients able to maintain target glycemic levels with diet, insulin, sulfonylurea, or metformin declined markedly over 9 years of follow-up (~50% of patients achieved target after 3 years of monotherapy; ~25% of patients achieved target after 9 years of monotherapy).<sup>(32)</sup> Thus, the ability of an agent to maintain glycemic control over the long-term is an important consideration when choosing therapy. If glycemic control cannot be maintained with oral agents alone, insulin may be added as well. <sup>(34)</sup> There are many obstacles to maintaining glycemic control in type 2 diabetes. Therefore, combination therapy should be promptly initiated.<sup>(35)</sup>

**Table 1. Therapeutic Options for the Treatment of Type 2 Diabetes**(30,35,36,37,38,39,40,41,42,43,44,45,46,47,48)

Class	Mechanism of Action	Advantages	Limitations	FDA Indications
Sulfonylureas <ul style="list-style-type: none"> <li>glyburide, glipizide, glimepiride</li> </ul>	↑ insulin secretion from the pancreas	-Decreases microvascular risk -Convenient daily dosing -Immediate onset of action	-Hypoglycemia -Weight gain -Hyperinsulinemia - Potential increased CV mortality risk	Monotherapy, Combo with insulin, metformin. TZDs, or α-glucosidase inhibitors
Biguanides <ul style="list-style-type: none"> <li>metformin</li> </ul>	Primary ↓ hepatic glucose production	-Weight loss -No hypoglycemia as monotherapy -Decreases macrovascular risk -Potential nonglycemic benefits -Convenient daily dosing	-Adverse GI effects -Contraindicated in patients with renal disease -Contraindicated in patients with CHF requiring pharmacologic treatment -Contraindicated in patients with acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma -Lactic acidosis risk (rare) -Should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials	Monotherapy, Combo with insulin, SU, meglitinides, or TZDs
<p>*This table is not meant to represent a comprehensive review of these agents. Please refer to the respective Prescribing Information for full details regarding these products; †As measured by homeostasis model assessment (HOMA). Combo = combination therapy; CV = cardiovascular; CHF = congestive heart failure; DPP-4 = dipeptidyl peptidase-4; GI = gastrointestinal; GLP-1 = glucagon-like peptide-1; LFT = liver function test; PPG = post-prandial glucose; T2DM = type 2 diabetes mellitus; TZD = thiazolidinedione; SU = sulfonylurea; SCr = serum creatinine; ESRD = end stage renal disease.</p>				

Class	Mechanism of Action	Advantages	Limitations	FDA Indications
$\alpha$ -glucosidase inhibitors <ul style="list-style-type: none"> <li>acarbose, miglitol</li> </ul>	↓ absorption of carbohydrates in the gut	<ul style="list-style-type: none"> <li>-Targets PPG</li> <li>-No hypoglycemia as monotherapy</li> <li>-Nonsystemic</li> </ul>	<ul style="list-style-type: none"> <li>-Dosed 3X/day</li> <li>-Adverse GI effects</li> <li>-No long term data</li> <li>-LFT monitoring (acarbose)</li> <li>-Limited information on severely renal impaired patients, SCr &gt; 2.0 mg/dL, therefore, treatment not recommended</li> <li>-Contraindicated in patients with inflammatory bowel disease, colonic ulceration or partial intestinal obstruction and in patients predisposed to intestinal obstruction</li> <li>-Contraindicated in patients with chronic intestinal diseases associated with disorders of digestion or absorption, or conditions that may deteriorate as a result of increased gas formation in the intestine</li> </ul>	Monotherapy, Combo with SU
<p>*This table is not meant to represent a comprehensive review of these agents. Please refer to the respective Prescribing Information for full details regarding these products; †As measured by homeostasis model assessment (HOMA). Combo = combination therapy; CV = cardiovascular; CHF = congestive heart failure; DPP-4 = dipeptidyl peptidase-4; GI = gastrointestinal; GLP-1 = glucagon-like peptide-1; LFT = liver function test; PPG = post-prandial glucose; T2DM = type 2 diabetes mellitus; TZD = thiazolidinedione; SU = sulfonylurea; SCr = serum creatinine; ESRD = end stage renal disease.</p>				

Class	Mechanism of Action	Advantages	Limitations	FDA Indications
Thiazolidinediones (TZDs) <ul style="list-style-type: none"> <li>rosiglitazone, pioglitazone</li> </ul>	Insulin sensitizer, ↑ peripheral glucose disposal	<ul style="list-style-type: none"> <li>-Minimal risk of hypoglycemia as monotherapy</li> <li>-Targets insulin resistance, a core defect of T2DM</li> <li>- Improves estimates of β-cell function</li> </ul>	<ul style="list-style-type: none"> <li>-Boxed Warning for Congestive Heart Failure</li> <li>-Boxed Warning for Myocardial Ischemia with rosiglitazone</li> <li>-Coadministration of rosiglitazone with insulin is not recommended</li> <li>-Use of rosiglitazone with nitrates is not recommended</li> <li>-Initiation of rosiglitazone is not recommended for patients experiencing an acute coronary event, discontinuation during this acute phase should be considered</li> <li>-Macular edema</li> <li>-Bone fracture</li> <li>-LFT monitoring</li> <li>-Weight gain, edema</li> <li>-Decrease in hemoglobin and hematocrit</li> <li>Rosiglitazone, in combination with other hypoglycemic agents, may increase the risk of hypoglycemia</li> <li>-Increased risk of pregnancy in premenopausal anovulatory women</li> </ul>	Monotherapy, Combo therapy with metformin and/or SU
Meglitinides/D-phenylalanine derivatives <ul style="list-style-type: none"> <li>nateglinide, repaglinide</li> </ul>	↑ insulin secretion from the pancreas	<ul style="list-style-type: none"> <li>-Targets PPG</li> <li>- Possible less hypoglycemia and weight gain than with SUs</li> </ul>	<ul style="list-style-type: none"> <li>-Dosed 3X/day</li> <li>-Hypoglycemia</li> <li>-Weight gain</li> <li>- Hyperinsulinemia</li> <li>-No long term data</li> <li>- Upper respiratory tract infection</li> </ul>	Monotherapy, Combo with metformin or TZDs
<p>*This table is not meant to represent a comprehensive review of these agents. Please refer to the respective Prescribing Information for full details regarding these products; †As measured by homeostasis model assessment (HOMA). Combo = combination therapy; CV = cardiovascular; CHF = congestive heart failure; DPP-4 = dipeptidyl peptidase-4; GI = gastrointestinal; GLP-1 = glucagon-like peptide-1; LFT = liver function test; PPG = post-prandial glucose; T2DM = type 2 diabetes mellitus; TZD = thiazolidinedione; SU = sulfonylurea; SCr = serum creatinine; ESRD = end stage renal disease.</p>				

Class	Mechanism of Action	Advantages	Limitations	FDA Indications
Incretin mimetics/ GLP-1 analogues • exenatide	↑ insulin secretion from the pancreas, ↓ glucagon secretion from the pancreas	-Sustained glycemic control -Weight loss -Improves estimates of $\beta$ -cell function	-Subcutaneous injection -Dosed twice daily -Adverse GI side effects - Post-marketing reports of acute pancreatitis Not recommended in patients with ESRD	Combo with metformin, SU, or TZD Combo with metformin and SU, or metformin and TZD
Dipeptidyl peptidase-4 (DPP-4) inhibitors • sitagliptin	Slow inactivation of GLP-1 ↑ insulin secretion from the pancreas, ↓ glucagon secretion from the pancreas	-No weight gain -Less hypoglycemia than SU's Good tolerability profile Improves estimates of $\beta$ -cell function	-Possibility for neurogenic and allergic reactions (theoretical) -Tolerability decreased with decreased DPP-4 specificity - Upper respiratory tract infections, nasopharyngitis, headache - Dosage adjustment with moderate or severe renal insufficiency	Monotherapy, Combo with metformin or TZD
*This table is not meant to represent a comprehensive review of these agents. Please refer to the respective Prescribing Information for full details regarding these products; †As measured by homeostasis model assessment (HOMA). Combo = combination therapy; CV = cardiovascular; CHF = congestive heart failure; DPP-4 = dipeptidyl peptidase-4; GI = gastrointestinal; GLP-1 = glucagon-like peptide-1; LFT = liver function test; PPG = post-prandial glucose; T2DM = type 2 diabetes mellitus; TZD = thiazolidinedione; SU = sulfonylurea; SCr = serum creatinine; ESRD = end stage renal disease.				

### Description of Alternate Treatment Options

The available literature demonstrates that several commonly used natural products can lower blood glucose in patients with diabetes. These products include N-acetylcysteine (NAC), pomegranate, coenzyme Q10, vitamin C, vitamin D, vitamin E, green tea, lutein, zeaxanthin, L-carnitine, cinnamon, magnesium, vanadium sulfate, nopal (prickly pear cactus), fenu-greek, karela (bitter melon), gymnema, ginseng, tronadora, chromium, and alpha-lipoic acid.<sup>(49,50)</sup>

Gene therapy/transplant (pancreas, islet cell) have more commonly been utilized in type 1 diabetes, but preliminary studies have evaluated its use in type 2 diabetes.<sup>(51)</sup>

## 4. PRODUCT DESCRIPTION

### 4.1 Generic Name, Brand Name and Therapeutic Class

**Generic Name:** rosiglitazone maleate and metformin HCl

**Brand Name:** Avandamet®

**Therapeutic Class:** fixed dose thiazolidinedione/biguanide tablets

### 4.2 Dosage Forms, Package Sizes, and NDC for All Formulations

National Drug Code/Availability:

- 2 mg/500 mg strength (pale pink, film coated oval tablet, debossed with gsk on one side and 2/500 on the other) :

- bottles of 60: 0007-3167-18
- 4 mg/500 mg strength (orange, film coated oval tablet, debossed with gsk on one side and 4/500 on the other):
  - bottles of 60: 0007-3168-18
- 2 mg/1000 mg strength (yellow, film coated oval tablet, debossed with gsk on one side and 2/1000 on the other):
  - bottles of 60: 0007-3163-18
- 4 mg/1000 mg strength (pink, film coated oval tablet, debossed with gsk on one side and 4/1000 on the other):
  - bottles of 60: 0007-3164-18

#### 4.3 AWP and WAC Cost per Unit

Wholesale Acquisition Cost (WAC)/tab:

- 2 mg/500 mg: \$1.85
- 4 mg/500 mg: \$3.13
- 2 mg/1000 mg: \$1.85
- 4 mg/1000 mg: \$3.13

#### 4.4 AHFS or Other Drug Classification

**AHFS Drug Classification:** 68:20.92 Miscellaneous Antidiabetic Agents

#### 4.5 FDA Approved Indications

*General*

[Refer to Enclosed Prescribing Information.](#)

Date of FDA Approval:

- Original Indication: October 10, 2002
- New dosage strengths of 2 mg/1000 mg, 4 mg/1000 mg: August 25, 2003

#### 4.6 Pharmacology

*General*

[Refer to Enclosed Prescribing Information.](#)

#### 4.7 Pharmacokinetics/Pharmacodynamics

[Refer to Enclosed Prescribing Information.](#)

#### 4.8 Contraindications

[Refer to Enclosed Prescribing Information.](#)

#### 4.9 Warnings/Precautions

##### **WARNINGS**

***Rosiglitazone maleate:* CONGESTIVE HEART FAILURE AND MYOCARDIAL ISCHEMIA**

- Thiazolidinediones, including rosiglitazone, cause or exacerbate congestive heart failure in some patients. After initiation of *Avandamet*, and after dose increases, observe patients carefully for sign and symptoms of heart failure (including excessive, rapid weight gain, dyspnea, and/or edema). If these signs and symptoms develop, the heart failure should be managed according to current standards of care. Furthermore, discontinuation or dose reduction of *Avandamet* must be considered.
- *Avandamet* is not recommended in patients with symptomatic heart failure. Initiation of *Avandamet* in patients with established NYHA Class III or IV heart failure is contraindicated.
- A meta-analysis of 42 clinical studies (mean duration 6 months; 14,237 total patients), most of which compared rosiglitazone to placebo, showed rosiglitazone to be associated with an



**increased risk of myocardial ischemic events such as angina or myocardial infarction. Three other studies (mean duration 41 months; 14,067 total patients), comparing rosiglitazone to some other approved oral antidiabetic agents or placebo, have not confirmed or excluded this risk. In their entirety, the available data on the risk of myocardial ischemia are inconclusive.**

#### ***Metformin hydrochloride: LACTIC ACIDOSIS***

- **Lactic acidosis is a rare, but serious complication that can occur due to metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic insufficiency, renal impairment and acute congestive heart failure.**
- **Symptoms include malaise, myalgias, respiratory distress, increasing somnolence and nonspecific abdominal distress. Laboratory abnormalities include low pH, increased anion gap and elevated lactate.**
- **If acidosis is suspected, discontinue *Avandamet* and hospitalize the patient immediately.**

[Refer to Enclosed Prescribing Information.](#)

#### **4.10 Adverse Events**

##### ***General***

[Refer to Enclosed Prescribing Information.](#)

#### ***The Risk of Myocardial Ischemic Events in Patients treated with Avandia***

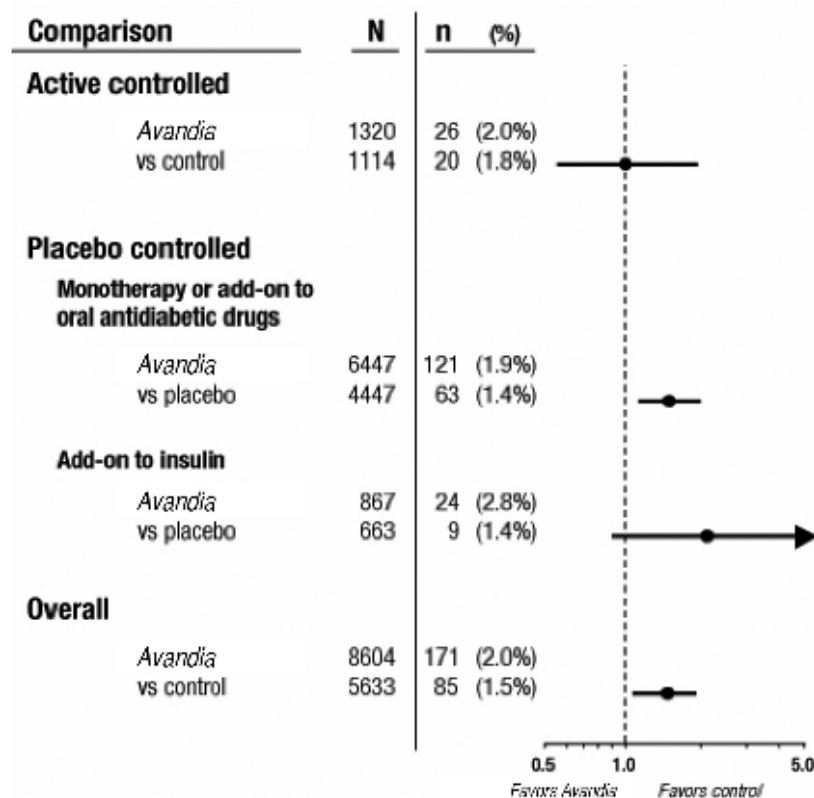
##### **FDA Meta-Analysis of Myocardial Ischemia in a Group of 42 Clinical Trials<sup>(42)</sup>**

A meta-analysis was conducted retrospectively to assess cardiovascular adverse events reported across 42 double-blind, randomized, controlled clinical trials (mean duration 6 months).<sup>(52)</sup> These studies had been conducted to assess glucose-lowering efficacy in type 2 diabetes, and prospectively planned adjudication of cardiovascular events had not occurred in the trials. Some trials were placebo-controlled and some used active oral antidiabetic drugs as controls. Placebo-controlled studies included monotherapy trials (*Avandia* monotherapy versus placebo monotherapy) and add-on trials (*Avandia* or placebo, added to sulfonylurea, metformin, or insulin). Active control studies included monotherapy trials (*Avandia* monotherapy versus sulfonylurea or metformin monotherapy) and add-on trials (*Avandia* plus sulfonylurea or *Avandia* plus metformin, versus sulfonylurea plus metformin). A total of 14,237 patients were included (8,604 in treatment groups containing *Avandia*, 5,633 in comparator groups), with 4,143 patient-years of exposure to *Avandia* and 2,675 patient-years of exposure to comparator. Myocardial ischemic events included angina pectoris, angina pectoris aggravated, unstable angina, cardiac arrest, chest pain, coronary artery occlusion, dyspnea, myocardial infarction, coronary thrombosis, myocardial ischemia, coronary artery disease, and coronary artery disorder. In this analysis, an increased risk of myocardial ischemia with *Avandia* versus pooled comparators was observed (2% *Avandia* versus 1.5% comparators, odds ratio [OR] 1.4, 95% confidence interval [CI] 1.1, 1.8). An increased risk of myocardial ischemic events with *Avandia* was observed in the placebo-controlled studies, but not in the active-controlled studies. (See Figure 1) A greater increased risk of myocardial ischemic events was observed in studies where *Avandia* was added to insulin (2.8% for *Avandia* plus insulin versus 1.4% for placebo plus insulin, [OR 2.1, 95% CI 0.9, 5.1]). This increased risk reflects a difference of 3 events per 100 patient years (95% CI -0.1, 6.3) between treatment groups.

In studies in which *Avandia* was added to insulin, *Avandia* increased the risk of congestive heart failure and myocardial ischemia.<sup>(42)</sup> Coadministration of *Avandia* and insulin is not recommended. In five, 26-week, controlled, randomized, double-blind trials which were included in the meta-analysis, patients with type 2 diabetes mellitus were randomized to coadministration of *Avandia* and insulin (N = 867) or insulin (N = 663). In these 5 trials, *Avandia* was added to insulin. These trials included patients with long-standing diabetes (median duration of 12 years) and a high prevalence of pre-existing medical conditions, including peripheral neuropathy, retinopathy, ischemic heart disease, vascular disease, and congestive heart failure. The total number of patients with emergent congestive heart failure was 21 (2.4%) and 7 (1.1%) in the *Avandia* plus insulin and insulin groups, respectively. The total number of patients with emergent myocardial ischemia was 24 (2.8%) and 9 (1.4%) in the *Avandia* plus insulin and insulin groups, respectively (OR 2.1 [95% CI 0.9, 5.1]). Although the event rate for congestive

heart failure and myocardial ischemia was low in the studied population, consistently the event rate was 2-fold or higher with coadministration of *Avandia* and insulin. These cardiovascular events were noted at both the 4 mg and 8 mg daily doses of *Avandia*.

**Figure 1. Forest Plot of Odds Ratios (95% Confidence Intervals) for Myocardial Ischemic Events in the Meta-Analysis of 42 Clinical Trials**



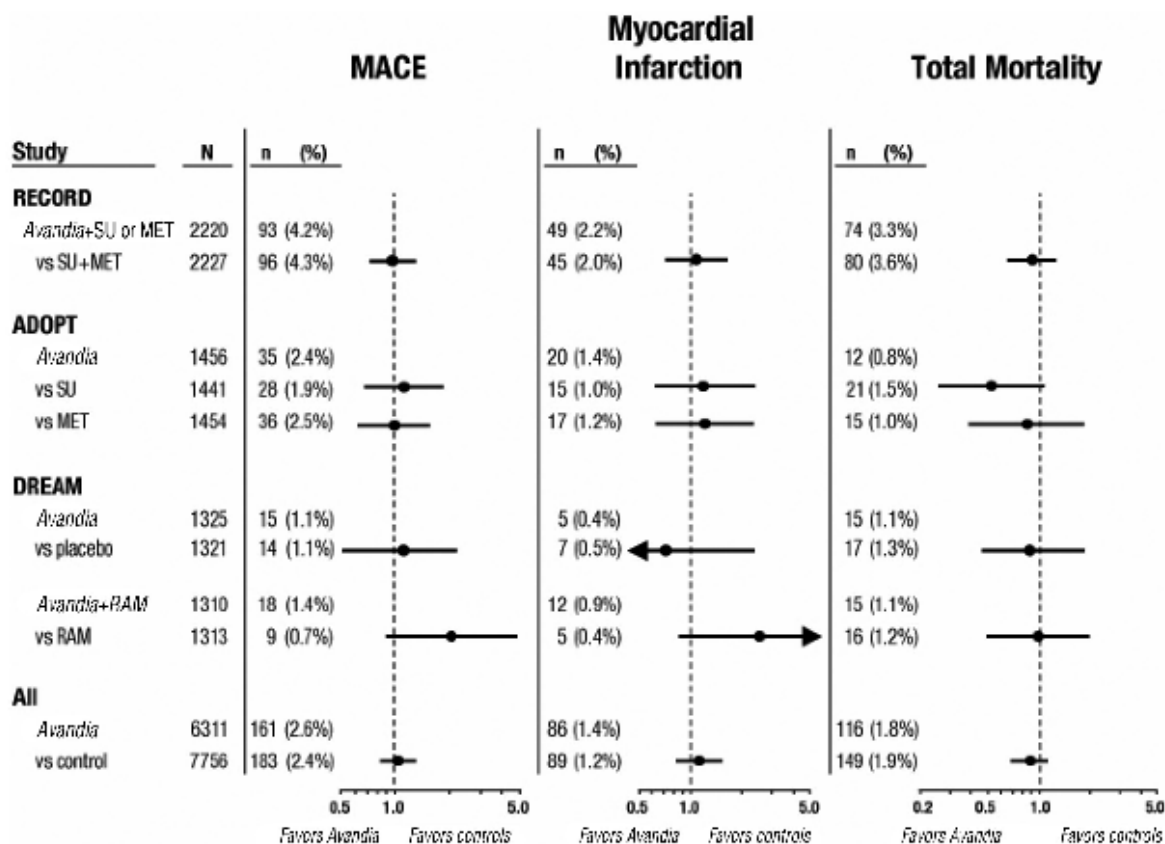
A greater increased risk of myocardial ischemia was also observed in patients who received *Avandia* and background nitrate therapy. For *Avandia* (N = 361) versus control (N = 244) in nitrate users, the odds ratio was 2.9 (95% CI 1.4, 5.9), while for non-nitrate users (about 14,000 patients total), the odds ratio was 1.3 (95% CI 0.9, 1.7). This increased risk represents a difference of 12 myocardial ischemic events per 100 patient years (95% CI 3.3, 21.4). Most of the nitrate users had established coronary heart disease. Among patients with known coronary heart disease who were not on nitrate therapy, an increased risk of myocardial ischemic events for *Avandia* versus comparator was not demonstrated. Use of *Avandia* with nitrates is not recommended.

#### **Myocardial Ischemic Events in Large Long-Term Prospective Randomized Controlled Trials of *Avandia*<sup>(42)</sup>**

Data from 3 other large long-term prospective randomized controlled clinical trials of *Avandia* were assessed separately from the meta-analysis. These 3 trials include a total of 14,067 patients (treatment groups containing *Avandia* N = 6,311, comparator groups N = 7,756), with patient-year exposure of 21,803 patient-years for *Avandia* and 25,998 patient-years for comparator. Duration of follow-up exceeded 3 years in each study. ADOPT (A Diabetes Outcomes Progression Trial) was a 4- to 6-year randomized, active-controlled study in recently diagnosed patients with type 2 diabetes naïve to drug therapy.<sup>(53)</sup> It was an efficacy and general safety trial that was designed to examine the durability of *Avandia* as monotherapy (N = 1,456) for glycemic control in type 2 diabetes, with comparator arms of sulfonylurea monotherapy (N = 1,441) and metformin monotherapy (N = 1,454). DREAM (Diabetes Reduction Assessment with Rosiglitazone and Ramipril Medication) was a 3- to 5-year randomized, placebo-controlled study in patients with impaired glucose tolerance and/or impaired fasting glucose.<sup>(54)</sup> It had a 2x2 factorial design, intended to evaluate the effect of *Avandia*, and separately of ramipril (an angiotensin converting

enzyme inhibitor [ACEI]), on progression to overt diabetes. In DREAM, 2,635 patients were in treatment groups containing *Avandia*, and 2,634 were in treatment groups not containing *Avandia*. Interim results have been published for RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes), an ongoing open-label, 6-year cardiovascular outcomes study in patients with type 2 diabetes with an average treatment duration of 3.75 years.<sup>(55)</sup> RECORD includes patients who have failed metformin or sulfonylurea monotherapy; those who have failed metformin are randomized to receive either add-on *Avandia* or add-on sulfonylurea, and those who have failed sulfonylurea are randomized to receive either add-on *Avandia* or add-on metformin. In RECORD, a total of 2,220 patients are receiving add-on *Avandia*, and 2,227 patients are on one of the add-on regimens not containing *Avandia*. For these 3 trials, analyses were performed using a composite of major adverse cardiovascular events (cardiovascular death, myocardial infarction, and stroke), referred to hereafter as MACE. This endpoint differed from the meta-analysis's broad endpoint of myocardial ischemic events, more than half of which were angina. Myocardial infarction included adjudicated fatal and nonfatal myocardial infarction plus sudden death. As shown in Figure 2, the results for the three endpoints (MACE, MI, and Total Mortality) were not statistically significantly different between *Avandia* and comparators.

**Figure 2. Hazard Ratios for the Risk of MACE (Myocardial Infarction, Cardiovascular Death, or Stroke), Myocardial Infarction, and Total Mortality With *Avandia* Compared With a Control Group**



SU = sulfonylurea; MET = metformin; RAM = ramipril

In preliminary analyses of the DREAM trial, the incidence of cardiovascular events was higher among subjects who received *Avandia* in combination with ramipril than among subjects who received ramipril alone, as illustrated in Figure 2. This finding was not confirmed in ADOPT and RECORD (active-controlled trials in patients with diabetes) in which 30% and 40% of patients respectively, reported ACE-inhibitor use at baseline.

In their entirety, the available data on the risk of myocardial ischemia are inconclusive. Definitive conclusions regarding this risk await completion of an adequately-designed cardiovascular outcome study.

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with *Avandia* or any other oral antidiabetic drug.

### **Reports of Gastrointestinal Adverse Drug Reactions with *Avandamet***

#### **Clinical Data**

##### **Pre-approval Studies**

During the 26-week, pre-approval, double-blind, clinical trials of *Avandia* in combination with metformin, diarrhea was the most commonly reported gastrointestinal (GI) adverse event in any of the treatment groups.<sup>(56,57)</sup> Diarrhea was reported in 12.7% (43/338) of patients treated with *Avandia* plus metformin compared to 15.6% (35/225) of patients treated with metformin, and in 2.3% (59/2526) of patients treated with *Avandia* monotherapy compared to 3.3% (20/601) of patients treated with placebo.

The following table shows various GI adverse events recorded from type 2 diabetic patients (double-blind population) who received *Avandia* in combination with metformin for 26 weeks (See Table 2).<sup>(56,57)</sup> In these trials, *Avandia* was administered in doses of 4 or 8 mg/day and metformin was administered in doses of 2500 mg/day.

**Table 2. GI Adverse Events During Pre-approval Combination Trials with *Avandia* and Metformin**  
(56,57) \*

Preferred Term†	<i>Avandia</i> + Metformin (N= 338)		Metformin (N= 225)	
	n	%	n	%
Diarrhea	43	12.7	35	15.6
Nausea	14	4.1	7	3.1
Abdominal pain	10	3.0	6	2.7
Flatulence	11	3.3	6	2.7
Dyspepsia	8	2.4	7	3.1
Vomiting	9	2.7	4	1.8
Anorexia	8	2.4	1	0.4
Constipation	5	1.5	2	0.9
Diverticulitis	3	0.9	2	0.9
Gastritis	2	0.6	0	0
Gastroenteritis	2	0.6	2	0.9
Gastroesophageal reflux	2	0.6	0	0
Hemorrhoids	2	0.6	2	0.9
Melena	2	0.6	1	0.4
* double-blind population				
† Preferred Term, WHO Body System (includes all terms occurring in $\geq 0.6\%$ of patients treated with <i>Avandia</i> and metformin)				
GI = Gastrointestinal				

In general, GI adverse events were of mild to moderate intensity with withdrawal rates of  $\leq 1.1\%$  and  $\leq 1.3\%$  with *Avandia* in combination with metformin and metformin monotherapy, respectively.<sup>(56,57)</sup>

##### **Additional Studies**

The efficacy and safety of adding *Avandia* 8 mg/day to sub-maximal doses of metformin (1000 mg/day) relative to uptitrated metformin monotherapy (2000 mg/day) was evaluated in a 24-week, randomized, double-blind, non-inferiority study involving over 700 patients with type 2 diabetes.<sup>(58)</sup> (11) A secondary objective of the study was to demonstrate that *Avandia* plus sub-maximal doses of metformin results in fewer gastrointestinal (GI) side effects compared to uptitrated metformin monotherapy.<sup>(58)</sup> The digestive health status index (DHSI) was used, a self-administered, disease-specific questionnaire that evaluates the existence and severity of gastrointestinal symptoms in five subscales: dysmotility, irritable bowel symptom (IBS)-diarrhea, IBS-constipation, IBS-pain, and IBS-gastroesophageal reflux disease (GERD)

plus ulcer. The DHSI is scored on a 0 to 100 scale, with higher scores indicating greater GI dysfunction. In comparison with uptitrated metformin monotherapy, patients in the *Avandia* plus sub-maximal metformin group reported significantly fewer GI symptoms of diarrhea, dysmotility, and GERD plus ulcer, as measured by the DHSI ( $P \leq 0.02$ ) (See Table 3). Both groups reported significantly more symptoms of constipation compared to baseline, however, there was no significant difference between treatment groups.

**Table 3. Mean Change from Baseline to Week 24 in the DHSI\*<sup>(58)</sup>**

	Mean Change from Baseline at 24 weeks				Treatment Effect
	Metformin 2000 mg/day		<i>Avandia</i> 4 mg BID + metformin 1000 mg/day		<i>Avandia</i> 4 mg BID + metformin 1000 mg/day
	n	(95% CI)	n	(95% CI)	(95% CI)
IBS-Diarrhea	277	11.64 (8.86, 14.43) ( $P < 0.0001$ )	269	0.49 (-1.79, 2.77) ( $P < 0.68$ )	-9.59 (-13.0, -6.18) ( $P < 0.0001$ )
IBS-GERD + ulcer	285	4.50 (2.65, 6.35) ( $P < 0.0001$ )	292	1.12 (-0.67, 2.91) ( $P < 0.22$ )	-3.22 (-5.70, -0.74) ( $P = 0.011$ )
IBS-Dysmotility	290	2.48 (1.09, 3.87) ( $P = 0.0005$ )	290	-0.46 (-1.70, 0.78) ( $P < 0.47$ )	-2.08 (-3.88, -0.28) ( $P < 0.024$ )
IBS-Constipation	290	2.89 (1.41, 4.37) ( $P = 0.0001$ )	292	1.77 (0.43, 3.09) ( $P < 0.01$ )	-0.39 (-2.25, 1.46) ( $P < 0.68$ )
IBS-Pain	261	4.10 (2.15, 6.04) ( $P < 0.0001$ )	254	1.58 (-0.35, 3.52) ( $P < 0.11$ )	-0.77 (-3.40, 1.87) ( $P < 0.06$ )
*Intent-to-treat population					
BID = twice daily; GI = gastrointestinal; DHSI = digestive health status index; GERD = gastroesophageal reflux disease; IBS = irritable bowel symptom					

Patients treated with *Avandia* plus submaximal metformin reported fewer GI adverse events than those treated with uptitrated metformin monotherapy [28.5% (109/382) vs. 39.1% (150/384), respectively].<sup>(58)</sup> The odds of experiencing a GI adverse event were 63% greater with uptitrated metformin monotherapy compared to *Avandia* plus submaximal metformin ( $P = 0.0023$ ).<sup>(11)</sup> Fewer patients in the combination group compared to those treated with uptitrated metformin monotherapy discontinued therapy due to GI effects (3.1% vs. 6.8%).

A 32-week, randomized, double-blind trial was conducted to evaluate the efficacy and safety of *Avandamet* compared to both *Avandia* and metformin monotherapies in drug naïve patients with type 2 diabetes.<sup>(9)</sup> The most commonly reported gastrointestinal adverse events included nausea/vomiting, diarrhea, and dyspepsia. (See Table 4)

**Table 4. On-therapy Gastrointestinal Adverse Events Reported by  $\geq 10\%$  of Patients<sup>(9)</sup>**

	<i>Avandamet</i> (n = 155)	<i>Avandia</i> (n = 159)	Metformin (n = 154)
	Number (%) patients		
Nausea/vomiting	25 (16)	13 (8)	20 (13)
Diarrhea	22 (14)	11 (7)	32 (21)
Dyspepsia	15 (10)	14 (9)	12 (8)

An open-label, 24 week, single-arm companion trial was conducted to evaluate the safety and efficacy of *Avandamet* in poorly-controlled patients with type 2 diabetes mellitus.<sup>(10)</sup> The most commonly reported GI adverse event with *Avandamet* therapy was diarrhea (12%).

Once a patient has been stabilized on any dose level of *Avandamet*, GI symptoms, which are common during initiation of metformin therapy, are unlikely to be drug related. Later occurrence of GI symptoms could be due to lactic acidosis or other serious disease.<sup>(8)</sup>

## Weight Gain with *Avandamet*

### Pre-approval Data

Dose-related weight gain has been seen with *Avandia* alone and in combination with other hypoglycemic agents. The mechanism of weight gain is unclear, but probably involves a combination of fluid retention and fat accumulation.

The effect of *Avandia* in combination with metformin on body weight was assessed from pooled data obtained from two 26-week double-blind trials.<sup>(56,57)</sup> In these trials, *Avandia* was administered either once or twice daily and was added to therapy of patients who were inadequately controlled on 2500 mg/day of metformin. Patients were excluded if they had a baseline body mass index (BMI) < 22 or > 38 kg/m<sup>2</sup> or had a variation in their weight > 10% between screening and baseline. At each visit, the patient's body weight was measured in normal clothing, without shoes. Results from these trials are presented in Table 5.

**Table 5. Weight Changes (kg) from Baseline During Clinical Trials with *Avandia* in Combination with Metformin<sup>(56,57)</sup>**

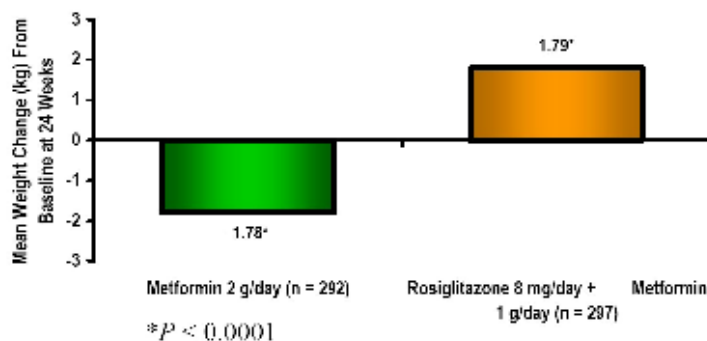
Double-blind, 26-Week Studies	
Regimen	Median (25th, 75th percentile)
<i>Avandia</i> 4 mg/day + Metformin n = 100	0.8 kg (-1.0, 2.6)
<i>Avandia</i> 8 mg/day + Metformin n = 184	2.1 kg (0, 4.3)
Metformin n = 175	-1.4 kg (-3.2, 0.2)

During the double-blind and open-label studies evaluating *Avandia* in combination with metformin, there were no reported cases of withdrawal due to weight gain.<sup>(56,57,59)</sup>

### Additional Studies

The efficacy and safety of adding *Avandia* 8 mg/day to submaximal doses of metformin (1000 mg/day) relative to uptitrated metformin monotherapy (2000 mg/day) was evaluated in a 24-week, double-blind study involving over 700 patients with type 2 diabetes.<sup>(11)</sup> At baseline, the mean body weight was 99.3 kg for the combination group (n = 297) and 96.9 kg in the uptitrated metformin group (n = 292). Fifty-five percent (162/297) of patients treated with *Avandia* and submaximal metformin experienced a weight gain of 0 to 2 kg at the end of the study. The mean change in weight from baseline to 24 weeks is presented below.

**Figure 3. Mean Change in Body Weight at 24 Weeks<sup>(11)</sup>**



Kelley et al compared *Avandia* 8 mg/day and metformin 2000 mg/day in 23 obese patients with type 2 diabetes for 4-months.<sup>(60)</sup> *Avandia* 8 mg/day (n = 11) resulted in a 1.1 kg increase in weight with a reduction in visceral fat by approximately 10% (-27 ± 13 cm<sup>2</sup>). Metformin (n = 12) resulted in a 2.7 kg weight loss but there was no change in visceral fat. Please note, abstracts are frequently based on early analyses and much of the information on study design and actual data have not been presented.

A 32-week, multicenter, randomized, double-blind study (Study 007) evaluated the safety and efficacy of *Avandamet* in 468 drug-naïve subjects (aged 18-70 yrs) with type 2 diabetes. <sup>(9)</sup> The median increase in weight from baseline (25th, 75th percentile) was 0.05 kg (-3.45, 3.0), 1.7 kg (-1.2, 4.5) and -2.2 kg (-5.5, -0.5) with *Avandamet*, rosiglitazone monotherapy, and metformin monotherapy, respectively. <sup>(9)</sup>

In a 24-week, open-label, companion trial (Study 004) with *Avandamet* in poorly controlled patients with type 2 diabetes, the mean increase in weight from baseline to 24 weeks was 2.6 kg. <sup>(10)</sup>

### Post-marketing Surveillance Data

In postmarketing experience, there have been reports of unusually rapid increases in weight and increases in excess of that generally observed in clinical trials. <sup>(42)</sup> Patients who experience such increases should be assessed for fluid accumulation and volume-related events such as excessive edema and congestive heart failure.

### Reports of Fluid Related Events with *Avandia*

#### Clinical Information

##### Edema

*Avandia* should be used with caution in patients with edema. <sup>(42)</sup> In controlled clinical trials of patients with type 2 diabetes, mild to moderate edema was reported in patients treated with *Avandia* (Table 6). The event usually did not require discontinuation of treatment with *Avandia* and tended to be reported more frequently at higher doses. Patients with ongoing edema are more likely to have adverse events associated with edema if started on combination therapy with insulin and *Avandia*. Coadministration of *Avandia* and insulin is not recommended.

**Table 6. Incidence of Edema with *Avandia* in Controlled Clinical Trials of Type 2 Diabetes Patients**

Treatment Group	N	%
<i>Avandia</i> monotherapy <sup>(42)*</sup>	2526	4.8
<i>Avandia</i> 4 or 8 mg/day + metformin <sup>(8)†</sup>	338	4.4
<i>Avandia</i> 8 mg/day + sulfonylurea <sup>(42)</sup>	885	12.4
<i>Avandia</i> 4 or 8 mg/day + metformin + sulfonylurea <sup>(61)</sup>	561	12.1
<i>Avandia</i> + insulin <sup>(42)‡</sup>	408	14.7
Placebo <sup>(42)</sup>	601	1.3
Metformin <sup>(42)</sup>	225	2.2
Sulfonylurea <sup>(42)</sup>	626	1.0
Metformin + sulfonylurea <sup>(61)</sup>	276	4.0
Insulin <sup>(42)</sup>	203	5.4

\*Includes all doses studied, majority of patients received *Avandia* 4 or 8 mg/day. †*Avandia* added to maximum doses of metformin. ‡Includes patients on *Avandia* 4 or 8 mg/day. Coadministration of *Avandia* and insulin is not recommended.

##### Congestive Heart Failure (CHF)

*Avandia*, like other thiazolidinediones, alone or in combination with other antidiabetic agents, can cause fluid retention, which may exacerbate or lead to heart failure. <sup>(42)</sup> Patients should be observed for signs and symptoms of heart failure. If these signs and symptoms develop, the heart failure should be managed according to current standards of care. Furthermore, discontinuation or dose reduction of *Avandia* must be considered. *Avandia* is not recommended in patients with symptomatic heart failure. Initiation of *Avandia* in patients with established NYHA Class III and IV heart failure is contraindicated.

In five, 26-week, controlled, randomized, double-blind trials, patients with type 2 diabetes were randomized to coadministration of *Avandia* and insulin (N = 867) or insulin (N = 663). <sup>(42)</sup> In these 5 trials, *Avandia* was added to insulin. These trials included patients with long-standing diabetes (median duration of 12 years) and a high prevalence of pre-existing medical conditions, including peripheral neuropathy, retinopathy, ischemic heart failure, vascular disease, and congestive heart failure. The total number of patients with emergent CHF was 21 (2.4%) and 7 (1.1%) in the *Avandia* plus insulin and insulin groups, respectively. These cardiovascular events were noted at both the 4 mg and 8 mg daily doses of *Avandia*. Coadministration of *Avandia* and insulin is not recommended.

Reports of CHF from an integrated clinical trials analysis (ICT), DREAM, ADOPT, and RECORD interim analysis remain consistent with previous reports and observations from individual and pooled controlled clinical trials of an increased incidence of CHF in patients treated with *Avandia*.<sup>(53,54,55,62)</sup>

### ***Avandia* vs. Placebo in Type 2 Diabetes Patients with NYHA Class I or II CHF**

A 52-week, double-blind, placebo-controlled, non-inferiority echocardiographic study was conducted in 224 patients with type 2 diabetes and NYHA Class I or II CHF.<sup>(63)</sup> Patients with an ejection fraction  $\leq 45\%$  treated with angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) and/or diuretics at study entry were randomized to *Avandia* (4 mg/day increased to 8 mg/day) or placebo in addition to background antidiabetic therapy. Background antidiabetic therapy included diet, exercise and/or oral monotherapy or oral combination therapy of no more than 2 medications (insulin therapy was excluded at entry to the study and was not permitted during the study except during acute episodes such as hospitalization, trauma, or infection to manage glycemic control).<sup>(63)</sup> The dose and regimen of oral antidiabetic therapy could be changed to achieve glycemic control. However, initiation or up-titration of metformin was not permitted during the study due to the risk of lactic acidosis. If a patient experienced signs or symptoms of fluid-retention or an exacerbation of CHF, CHF medications could be adjusted by optimizing diuretic therapies, adjusting background ACEI/ARB therapy, adding cardiac glycosides, or the dose of *Avandia* could be reduced.

An independent committee conducted a blinded evaluation of fluid-related events (including CHF) and cardiovascular hospitalizations according to predefined criteria (adjudication).<sup>(63)</sup> Separate from the adjudication, other cardiovascular adverse events were reported by investigators. Although no treatment difference in change from baseline of ejection fractions was observed, more cardiovascular adverse events were observed with *Avandia* compared to placebo during the 52-week study (Table 7).

**Table 7. Emergent Cardiovascular Adverse Events (Study 211)<sup>(63)</sup>**

EVENTS	<i>Avandia</i> N = 110 n (%)	Placebo N = 114 n (%)	P-value
<b>Major Adjudicated Clinical Endpoints</b>			
Cardiovascular Death	5 (4.8)	4 (3.8)	0.85
All-cause Mortality	8 (7.7)	5 (4.8)	0.48
All-cause Mortality or Worsening CHF	11 (10.6)	8 (7.5)	0.59
<b>Other Adjudicated Clinical Endpoints</b>			
Cardiovascular Hospitalization*	21 (19.1)	15 (13.2)	0.47
Definite Worsening CHF	5 (4.5)	4 (3.5)	0.86
Possible Worsening CHF	2 (1.8)	0	N/A †
New or Worsening Edema	28 (25.5)	10 (8.8)	0.01
New or Worsening Dyspnea	29 (26.4)	19 (16.7)	0.20
Increase in CHF Medication	36 (32.7)	20 (17.5)	0.04
* Major reasons for cardiovascular hospitalization included worsening of CHF, myocardial infarction, and stroke/transient ischemic attack † No events occurred in one treatment group, preventing analysis using this model			

### ***Reports of Macular Edema with Avandia***

Post-marketing reports of new-onset or worsening diabetic macular edema with decreased visual acuity have been reported with *Avandia*. Many of these patients reported concurrent peripheral edema. In some cases, the visual events resolved or improved following discontinuation of the drug.

### **Background**

Macular edema typically occurs in association with diabetic retinopathy, although it is more likely to occur as retinopathy progresses.<sup>(64)</sup> Diabetic macular edema is a swelling of the retina that occurs after breakdown of the blood-retinal barrier because of leakage of dilated hyperpermeable capillaries and microaneurysms within the macula (the central portion of the retina).<sup>(65)</sup> Risk factors for macular edema include duration of diabetes, presence of retinopathy, hypertension, and poor glycemic control.<sup>(64) (65)</sup>



## Clinical Data

In a retrospective chart review, Ryan et al identified 30 type 2 diabetic patients using a TZD who had both lower extremity edema that increased since starting the TZD and clinically significant macular edema.<sup>(66)</sup> Eleven patients received *Avandia*, 17 patients received Actos® (pioglitazone hydrochloride), and 2 patients received both TZDs at different times. Clinically significant macular edema was documented by clinical examination as well as review of color photographs and fluorescein angiograms. Fluid retention was noted to be present or absent. Response to TZD cessation was measured by reported weight loss, clinical estimation of lower extremity edema, visual acuity changes, and change in macular edema. Therapeutic ocular intervention included focal laser treatment and therapeutic systemic intervention included TZD cessation, diuresis, and dialysis (1 case).

Of the 30 type 2 diabetes patients (average duration since diagnosis: 8.3 years), 23 patients also had hypertension, 6 patients had heart failure, and 1 patient had renal failure. <sup>(66)</sup> Additionally, 2 patients were on TZD monotherapy, 12 patients were receiving other oral antidiabetic medications with the TZD, 7 patients were receiving insulin in combination with the TZD, 7 patients were receiving other oral antidiabetic medications and insulin with the TZD, and 2 patients had no information available. Clinically significant macular edema was bilateral in 24 patients and unilateral in 6 patients. Macular laser photocoagulation was performed on 26 patients (48/60 eyes;  $\geq 2$  times in 22/60 eyes). Fluorescein angiography and clinical evaluation by a physician determined that the macular edema was diffuse in at least 1 eye of 19/30 patients, with 17/30 patients having bilateral diffuse macular edema. Average patient-reported weight gain while on the TZD was 23 lbs. Average patient-reported weight loss following TZD cessation was 19 lbs.

Decreased lower extremity edema was observed in all 11 patients followed for  $> 3$  months after TZD cessation. <sup>(66)</sup> Ten of 11 patients also reported weight loss after TZD cessation. In these 11 patients, the average patient-reported weight gain was 30 lbs (range, 15-50 lbs) while on the TZD. The average patient-reported weight loss was 19 lbs (range 0-30 lbs) following TZD cessation. Of these 11 patients, 10 had hypertension, 3 developed renal failure, and 3 had heart failure. Reduction in macular edema occurred in  $< 3$  months in 4/11 patients and in 8/11 patients over a 1- to 2-year period. These results should be interpreted with caution due to the retrospective nature of the analysis and the limitations inherent in such an analysis.

GlaxoSmithKline vigilantly monitors the safety of all of its products. As part of this monitoring, postmarketing reports of new onset or worsening (diabetic) macular edema have been received for some diabetic patients taking rosiglitazone or another thiazolidinedione (TZD). Some patients presented with blurred vision or decreased visual acuity, but some patients appear to have been diagnosed on routine ophthalmologic examination. Most patients had peripheral edema at the time macular edema was diagnosed. Some patients had improvement in their macular edema after discontinuation of their TZD. Patients with diabetes should have regular eye exams by an ophthalmologist, per the Standards of Care of the American Diabetes Association. Additionally, any diabetic patient who reports any kind of visual symptom should be promptly referred to an ophthalmologist, regardless of the patient's underlying medications or other physical findings<sup>(42)</sup>.

## *Avandia and Fractures*

### Background

Over the last 20 years, data has been reported that indicates patients with type 2 diabetes are at increased risk of nonvertebral fracture, particularly fractures of the hip, arm and foot.<sup>(67,68,69,70)</sup> Elderly diabetic women are up to 6 times more likely to have a hip fracture than elderly nondiabetic women; the corresponding figure for elderly diabetic men is even higher (up to 8-fold higher risk).<sup>(71)</sup> The reason for this is unclear, particularly since type 2 diabetes tends to be associated with above average bone density and thus might be expected to be protective against osteoporosis and fracture.<sup>(70)</sup> Type 2 diabetes is known to be a predisposing factor for disability and falls in the elderly, and this predisposition has been postulated to account for some of the fractures.<sup>(72,73)</sup> However, even after adjusting for the frequency of falls, the fracture risk for diabetic patients persists.<sup>(70)</sup> Further information regarding fracture risk in type 2 diabetes is provided by analysis of data from the Women's Health Initiative Observational Study (WHIOS). <sup>(70)</sup> The WHIOS study enrolled a racially diverse group of over 93,000 postmenopausal women, collected detailed

information on risk factors for fracture, and followed up this population for incident falls and fractures. A separate analysis of fracture data at various skeletal sites was conducted among the subgroup of 5,285 postmenopausal females (age 50-79 years; mean 64.9 years) with type 2 diabetes who participated in this study. Information on antidiabetic drug use in this patient population was limited to insulin, which was being taken by 17% of patients on study entry. Over the 7 year follow-up period, women with diabetes were 29% more likely to have a fracture of any type than women without diabetes.

### Clinical Information

The ADOPT (A Diabetes Outcome Progression Trial) trial was designed to measure the long-term durability of glycemic control in people recently diagnosed with type 2 diabetes ( $\leq 3$  years) receiving monotherapy with *Avandia* versus metformin or glyburide.<sup>(53)</sup> Among the 4,351 people with type 2 diabetes involved in ADOPT and treated for a median of 4 years, 200 people reported to experience at least one bone fracture event: 92 in the *Avandia* group (6.3% or 1.86 per 100 patient years); 59 in the metformin group (4.1% or 1.20 per 100 patient years) and 49 in the glyburide group (3.4% or 1.15 per 100 patient years).<sup>(74)</sup> The estimated hazard ratios [with 95% confidence interval (CI)] for the risk of fracture with *Avandia* versus metformin and glyburide were 1.57 (1.13, 2.17;  $P = 0.0073$ ) and 1.61 (1.14, 2.28;  $P = 0.0069$ ), respectively.

Men and women randomized to the three treatment groups were well matched at baseline.<sup>(74)</sup> The majority of women in the study were  $>50$  years old (71%) and postmenopausal (77%) by self report. Please refer to Table 8. There were no clear differences in the pattern of use of concomitant medications, estrogen containing hormones, calcium supplements, bisphosphonates, thiazide and loop diuretics, or glucocorticoids, between women who did and did not report fracture within any treatment group.

**Table 8. Fracture Rates Reported in Women by Menopausal Status and Age<sup>(74)</sup>**

	<i>Avandia</i>			Metformin			Glyburide		
Pre-menopausal n† (%)	10/147 (6.8)			4/127 (3.2)			3/156 (1.9)*		
Post-menopausal n‡ (%)	50/498 (10.0)			26/463 (5.6)*			18/449 (4.0)*		
	With Fracture N = 60	Without Fracture N = 585	P Value	With Fracture N = 30	Without Fracture N = 560	P Value	With Fracture N = 21	Without Fracture N = 584	P Value
Age $\leq 50$ n (%)	11 (18.3)	181 (30.9)	0.065	8 (26.7)	153 (27.3)	0.954	3 (14.3)	176 (30.1)	0.012
Age $> 50$ - $\leq 60$ n (%)	24 (40.0)	205 (35.0)		11 (36.7)	203 (36.3)		5 (23.8)	197 (33.7)	
Age $> 60$ n (%)	25 (41.7)	199 (34.0)		11 (36.7)	204 (36.4)		13 (61.9)	211 (36.1)	

\* $P < 0.05$  vs. *Avandia*; † n = number of premenopausal women that reported a fracture/total number of premenopausal women; ‡ n = number of postmenopausal women that reported a fracture/total number of postmenopausal women.

Of the 1,840 women in ADOPT, 111 experienced at least one bone fracture event, predominantly in the upper and lower limb.<sup>(74)</sup> These sites of fracture are different from those usually associated with postmenopausal osteoporosis (e.g., hip or spine). Of these, 60 women were in the *Avandia* group (9.3% or 2.74 per 100 patient years); 30 were in the metformin group (5.1% or 1.54 per 100 patient years) and 21 were in the glyburide group (3.5% or 1.29 per 100 patient years). The hazard ratios (with 95% CI) for the risk of fracture with *Avandia* versus metformin and glyburide in women were 1.81 (1.17, 2.80;  $P = 0.008$ ) and 2.13 (1.30, 3.51;  $P = 0.0029$ ), respectively. There was no increased risk of fracture with *Avandia* over

the first 12 months of treatment, the increased risk manifested beyond 12 months of exposure. Amongst women that experienced a fracture event, 11.7%, 16.7%, and 23.8% reported accidental limb injury or fall within 30 days prior to the fracture and 18.3%, 16.7%, 14.3% reported more than one fracture in the *Avandia*, metformin, and glyburide groups, respectively. Please refer to Table 9. The observed fracture rates from ADOPT appear to be within the range seen in a literature based review of observational studies in women with diabetes and upon analysis of large managed care databases. (67,70,75,76)

There were no statistically significant differences observed among treatment groups in ADOPT in the number of fractures reported in men.<sup>(74)</sup> The hazard ratios for the risk of fracture with *Avandia* versus metformin and glyburide in men were 1.18 (0.72, 1.96;  $P = 0.5115$ ) and 1.08 (0.65, 1.79;  $P = 0.7680$ ), respectively.

**Table 9. Patients with Fractures in ADOPT<sup>(74)</sup>**

MALE PATIENTS	<i>Avandia</i>		Metformin		Glyburide	
	811 Males		864 Males		836 Males	
	n (%)	Rate/100 PY	n (%)	Rate/100 PY	n (%)	Rate/100 PY
Experienced a fracture	32 (4.0)	1.16	29 (3.4)	0.98	28 (3.4)	1.07
FEMALE PATIENTS	645 Females		590 Females		605 Females	
	n (%)	Rate/100 PY	n (%)	Rate/100 PY	n (%)	Rate/100 PY
Experienced a fracture*	60 (9.3)	2.74	30 (5.1)	1.54	21 (3.5)	1.29
<i>Lower limb</i> †	36 (5.58)	1.65	18 (3.05)§	0.92	8 (1.32)§	0.49
Hip	2 (0.31)	0.09	2 (0.34)	0.1	0	0
Foot	22 (3.41)	1.01	7 (1.19)§	0.36	4 (0.66)§	0.25
<i>Upper limb</i> ‡	22 (3.41)	1.01	10 (1.70)	0.51	9 (1.49)	0.55
Hand	8 (1.24)	0.37	4 (0.68)	0.21	1 (0.17)	0.06
Humerus	5 (0.78)	0.23	0	0	0	0
Wrist	5 (0.78)	0.23	3 (0.51)	0.15	4 (0.66)	0.25
<i>Spine</i>	1 (0.16)	0.05	1 (0.17)	0.05	1 (0.17)	0.06

\* Some patients experienced fractures in more than one category; †Other sites of fracture included: ankle, femur, fibula, lower limb (general), patella, and tibia; ‡Other sites of fracture included: clavicle, forearm, radius, and upper limb (general).

n = number of patients; Rate/100 PY = Patients with events per 100 patient years.

§  $P < 0.05$  vs. *Avandia*

An independent safety committee reviewed an interim analysis of fractures in another large ongoing, long-term, controlled rosiglitazone clinical trial. The primary purpose of that study is to investigate cardiovascular endpoints in patients with type 2 diabetes mellitus. The results of the preliminary analysis were reported to GlaxoSmithKline as being consistent with the observations from ADOPT. The independent safety committee also recommended that the study continue without modification. Final results of this study are anticipated to be available in 2009.

### Long-term use of thiazolidinediones and fractures in type 2 diabetes: a meta-analysis

Loke and colleagues assessed the risk of fractures in patients with impaired glucose tolerance (IGT) or type 2 diabetes with the long-term ( $\geq 1$  year) use of thiazolidinediones (TZDs).<sup>(77)</sup> This analysis evaluated 10 randomized controlled trials ( $N = 13,715$ ) and 2 observational studies ( $N = 31,679$ ) through June 2008 that described the risk of fracture or change in bone density with TZDs. Long-term randomized controlled trials and observational studies that described the risk of fracture with any TZD (*Avandia*, pioglitazone, or troglitazone) were included in the analysis. The secondary outcome evaluated the effects of TZD therapy on bone mineral density (BMD). In this analysis, randomized controlled trials and observational studies of any duration that compared changes in bone mineral density in patients with and without TZD exposure were evaluated.

Pooled data from the 10 randomized controlled trials evaluated the risk of fractures associated with TZD therapy. As compared to the control, TZD therapy significantly increased the risk of overall fractures, (Odds Ratio[OR] 1.45, 95% Confidence Interval [CI] 1.18-1.79;  $P < 0.001$ ) Additionally, data from 5 randomized trials reported that TZD therapy significantly increased the risk of fracture among women

compared to control (OR 2.23, 95% CI 1.65-3.01;  $P < 0.001$ ). Therapy with TZDs did not increase the risk of fracture risk among men (OR 1.00, 95% CI 0.73-1.39;  $P = 0.98$ ).

A correlation between TZD exposure and fractures was also reported in 2 observational studies. A case-controlled study demonstrated a significant association between TZD exposure (current users with > eight prescriptions) and fractures among women (OR 2.56, 95% CI 1.43-4.58). Additionally, a separate cohort study reported that *Avandia* was significantly associated with fractures when compared to women taking metformin (OR 1.38, 95% CI 1.03-1.82). However, no greater fracture risk was seen in the comparison of *Avandia* and sulfonylurea (OR 0.89, 95% CI 0.69-1.14). In either study, there was no significant association with TZD exposure and fractures among men.

A change in BMD was identified in two randomized controlled trials and two observational studies. TZD therapy was associated with a consistent decline in BMD as compared with controls. A significant reduction in BMD at the lumbar spine and at the hip was observed among women who used TZD therapy. The percent change in BMD with weighted mean difference was -1.11% (95% CI -2.08 to -0.14%;  $P = 0.02$ ) and at the hip the weighted mean difference was -1.24% (95% CI -2.34% to -0.67%;  $P < 0.001$ ).

The investigators interpretation of this data stated that long-term use of TZDs doubles the risk of fractures among women with type 2 diabetes, without a significant increase in risk of fractures among men with type 2 diabetes.

#### **Observational Study Exploring Fractures with Thiazolidinedione Use**

An observational, nested, case-controlled study in a UK-based general practice research database compared the risk of fractures in men and women with type 2 diabetes receiving thiazolidinediones (TZDs) to those on other oral antidiabetic drugs (OADs).<sup>(78)</sup> Between January 1994 and December 2005, individuals who received at least one prescription for a TZD, sulfonylurea, biguanide, alpha glucosidase inhibitor, or prandial glucose regulator, with or without concomitant insulin use ( $n = 50,048$ ) and adults with type 2 diabetes who never received a prescription for an OAD or insulin ( $n = 16,648$ ) were identified as study population. From this population, 1,020 patients with a first time diagnosis of low trauma fractures were identified and 3,728 control subjects without fracture diagnosis were randomly selected to match patients with fracture.

Clinically diagnosed low-trauma fractures consisted of wrist/forearm (301), hip (274), humerus (222), rib (148), vertebral (56) and others (19).<sup>(78)</sup> Of the 1,020 case patients with fracture, 65 subjects used thiazolidinediones (TZDs), all in combination with other oral antidiabetic drugs (OADs). After adjustments, including age, body mass index, other antidiabetic drugs, concomitant medications, and comorbidities, the odds ratio (OR) for current users of 8 or more TZD prescriptions, corresponding to 12-18 months of therapy, compared with non users was 2.43 [95% confidence interval (CI): 1.49 – 3.95]. The highest risk estimate was seen in users of 15 or more prescriptions, corresponding to 2 or more years of therapy [2.86 (95% CI: 1.57 - 5.22);  $P < 0.001$ ]. The adjusted odds ratio on fracture risk for current users of 8 or more prescriptions of *Avandia* or pioglitazone was 2.38 (95% CI: 1.39 - 4.09) and 2.59 (95% CI: 0.96 - 7.01), respectively. In addition, the adjusted odds ratio for current users of 8 or more TZD prescriptions stratified by sex was 2.50 (95% CI 0.84-7.41) for men and 2.56 (95% CI 1.43-4.58) for women. In contrast to the observations in ADOPT (A Diabetes Outcome Progression Trial), risk of fracture also increased in men and TZD use was associated with an increased risk of hip and nonvertebral osteoporosis fractures in both men and women.

#### **4.11 Other Clinical Considerations**

[Refer to Enclosed Prescribing Information.](#)

#### **4.12 Drug/Food/Disease Interactions**

[Refer to Enclosed Prescribing Information.](#)

#### **4.13 Dosing and Administration**

[Refer to Enclosed Prescribing Information.](#)

#### **4.14 Co-prescribed/Concomitant Therapies**

[Refer to Enclosed Prescribing Information.](#)

## 5. EFFICACY AND SAFETY TRIALS (FDA APPROVED)

### 5.1 Efficacy and Safety of *Avandia* Add-on Therapy with Metformin in Type 2 Diabetes

The use of *Avandia* in combination with metformin was evaluated in two pivotal, 26-week, randomized, double-blind studies involving over 670 patients with type 2 diabetes. <sup>(56,57)</sup> Patients in both studies were randomized to one of three treatment regimens (described in Table 10) after completing the following steps:

- **Metformin Titration Period** - Patients naïve to metformin and those entering the study on sub-maximal doses of metformin entered a dose escalation period. Doses were increased by 500 mg/week to a maximum dose of 2500 mg/day.
- **Metformin Maintenance/Placebo Run-In Period** – Patients then entered a 4-week trial of diet/exercise reinforcement in addition to the maximum recommended metformin dose (2500 mg/day) in order to identify those patients who were inadequately controlled (fasting plasma glucose [FPG]  $\geq 140$ mg/dL and  $\leq 300$ mg/dL). Only those patients inadequately controlled on metformin therapy were eligible for randomization.

*Avandia* 4 or 8 mg/day in combination with metformin significantly reduced HbA1c and FPG compared to baseline and metformin alone. The most common adverse events (>5%) reported in patients treated with *Avandia* in combination with metformin were upper respiratory tract infection, injury, headache, fatigue, sinusitis, diarrhea and anemia. Overall, these events were generally mild to moderate in severity and usually did not require discontinuation of treatment. A summary of the efficacy and safety results are presented in Table 10 and Table 11.

**Table 10. Evaluation of *Avandia* in Combination with Metformin - Pivotal Clinical Studies <sup>(56,57)</sup>**

Study Design/ Baseline Characteristics	n (ITT)	Regimen	Baseline HbA1c (%) / FPG (mg/dL)	Primary Endpoint HbA1c (%)		Secondary Endpoints FPG (mg/dL)	
				Mean Difference from Baseline	Mean Dif- ference from Com- parator	Mean Difference from Baseline	Mean Differ- ence from Compara- tor
<b>Study 094</b>  26-week, R, DB, PC Age 58 yrs, 68% male, BMI 30 kg/m <sup>2</sup> , 80% white, duration of disease: 8 yrs, U.S.	113	MET + PBO	8.6/214	0.5*	NA	6	NA
	116	RSG 4 mg QD + MET	8.9/215	-0.6*	-1.0*	-33*	-40*
	110	RSG 8 mg QD + MET	8.9/220	-0.8*	-1.2*	-48*	-53*

BMI = body mass index; DB = double-blind; FPG = fasting plasma glucose; ITT = intent-to-treat; MET = metformin; NA = not applicable; PBO = placebo; PC = placebo-controlled; R= randomized; RSG = rosiglitazone; URTI= upper respiratory tract infection; U.S. = United States.

\*  $P < 0.0001$ ; †  $P < 0.0001$  vs. *Avandia* + MET; ‡ n = 103 for HbA1c; § A rise in HbA1c in the *Avandia* plus placebo and metformin plus placebo groups was observed in this study. These results may reflect the particular design of the study. Approximately 50% of patients had been previously treated with more than one oral antidiabetic agent. Combination therapy was withdrawn at study entry, and patients were titrated to maximal dose metformin. Only patients inadequately controlled on maximal dose metformin were then randomized. Because of the limitations in study design, comparisons between the two monotherapy arms in this study are not appropriate.

Study Design/ Baseline Characteristics	n (ITT)	Regimen	Baseline HbA1c (%) / FPG (mg/dL)	Primary Endpoint HbA1c (%)		Secondary Endpoints FPG (mg/dL)	
				Mean Difference from Baseline	Mean Dif- ference from Com- parator	Mean Difference from Baseline	Mean Dif- ference from Compara- tor
<b>Study 093</b> 26-week, R, DB, Age 59 yrs, 61% male, BMI 31 kg/m <sup>2</sup> , 79% white, duration of disease: 7 yrs, U.S.	106	MET + PBO	8.8/210	0.1	-0.8†	6	-56†
	95	RSG 4 mg BID + PBO	8.7/206	1.3*	-2.0†	30*	-80†
	105‡	RSG 4 mg BID + MET §	8.7/217	-0.7*	NA	-52*	NA
BMI = body mass index; DB = double-blind; FPG = fasting plasma glucose; ITT = intent-to-treat; MET = metformin; NA = not applicable; PBO = placebo; PC = placebo-controlled; R= randomized; RSG = rosiglitazone; URTI= upper respiratory tract infection; U.S. = United States.							
* $P < 0.0001$ ; † $P < 0.0001$ vs. <i>Avandia</i> + MET; ‡ n = 103 for HbA1c; § A rise in HbA1c in the <i>Avandia</i> plus placebo and metformin plus placebo groups was observed in this study. These results may reflect the particular design of the study. Approximately 50% of patients had been previously treated with more than one oral antidiabetic agent. Combination therapy was withdrawn at study entry, and patients were titrated to maximal dose metformin. Only patients inadequately controlled on maximal dose metformin were then randomized. Because of the limitations in study design, comparisons between the two monotherapy arms in this study are not appropriate.							

**Table 11. Adverse Events Reported During the Pivotal Clinical Studies of *Avandia* in Combination with Metformin<sup>(56,57)\*</sup>**

	RSG 4 mg/day + MET	RSG 8 mg/day‡ + MET	RSG 8 mg/day§	MET
	N = 119	N = 219	N = 107	N = 225
Preferred Term	%	%	%	%
URTI	16	16	17.8	8.9
Diarrhea	12.6	12.8	4.7	15.6
Anemia	5.9	7.8	0.9	2.2
Injury†	10.1	6.8	12.1	7.6
Sinusitis	5	6.8	4.7	5.3
Headache	6.7	6.4	4.7	8.9
Back Pain	3.4	5.9	2.8	4
Fatigue	6.7	5.5	4.7	4
Arthralgia	5	5	1.9	2.2
Pain	3.4	4.6	6.5	4
Infection Viral	5.9	4.6	3.7	3.6
Nausea	5	3.7	2.8	3.1
Urinary Tract Infection	3.4	2.7	5.6	3.1
Hypercholesterolemia	1.7	2.3	7.5	1.3
Hyperglycemia	2.5	1.8	16.8	4.4
Hypertension Aggravated	2.5	0.9	0.9	5.3
Micturition Frequency	0.8	0.9	5.6	2.2
MET = metformin; RSG = rosiglitazone; URTI = upper respiratory tract infection.				
* Pooled results of on-therapy adverse events occurring in > 5% of patients in any treatment group; † Injury includes items such as cuts, burns, sprains, fractures, accidents, and surgical procedures; ‡ Patients may have received the total dose once daily or in divided doses twice daily; § treatment arm included in Study 093.				

Gomez-Perez et al conducted a 26-week, randomized, double-blind, placebo-controlled study in 116 Mexican patients to evaluate the efficacy and safety of *Avandia* in combination with metformin. <sup>(79)</sup> Patients inadequately controlled with metformin 2500 mg/day, continued on open-label metformin and were randomized in a double-blind manner to add-on therapy with *Avandia* 2 mg twice daily, *Avandia* 4 mg twice daily, or placebo. All analyses were conducted with the intent-to-treat group that included 105 patients. Baseline characteristics were similar in the three groups. A summary of glycemic efficacy results are presented in Table 12.

**Table 12. Glycemic Results in Mexican Patients at 26 weeks <sup>(79)</sup>**

	RSG 2 mg BID + MET N = 35	RSG 4 mg BID + MET N = 36	PBO + MET N = 34
Mean change from baseline HbA1c (%)	-0.7*	-1.2*	0.3
Difference from metformin + placebo (%)	-1.0*	-1.5†	-
% Responders‡	54%	61%	24%
BID= twice daily; MET = metformin; PBO = placebo; RSG = rosiglitazone			
* $P < 0.05$ ; † $P < 0.001$ ; ‡ Patients who achieved an HbA1c response defined as $\geq 0.7\%$ reduction from baseline.			

The mean FPG decreased significantly from baseline with *Avandia* 2 mg twice daily plus metformin (-45 mg/dL,  $P < 0.0009$ ) and *Avandia* 4 mg twice daily plus metformin (-63 mg/dL,  $P < 0.0001$ ) but increased with metformin plus placebo (+4 mg/dL,  $P = 0.7143$ ). <sup>(79)</sup> Target FPG values ( $< 140$  mg/dL) were achieved in 26%, 42%, and 6% of patients who received *Avandia* 2 mg twice daily plus metformin, *Avandia* 4 mg twice daily plus metformin and placebo plus metformin, respectively.

The number of adverse events was similar between groups. <sup>(79)</sup> Gastrointestinal events (diarrhea, nausea, vomiting, flatulence, or abdominal pain) were reported in 17% and 15% of *Avandia* and placebo-treated patients, respectively. Overall, edema was reported in 5% of patients who received *Avandia* and metformin, but none of the events were considered serious or resulted in study withdrawal. Four cardiac-related adverse events were reported in the study which included 1 report of bundle branch block, 1 report of myocardial ischemia, and 2 reports of bundle branch block and tachycardia in the placebo-treated, *Avandia* 2 mg plus metformin and *Avandia* 4 mg plus metformin groups, respectively. None of these cardiac-related adverse events were considered serious or resulted in study withdrawal. Mean weight increased from baseline with *Avandia* (2 mg twice daily: +0.26 kg; 4 mg twice daily: +2.42 kg) and decreased in the placebo group (-0.86 kg).

The use of *Avandia* in combination with metformin was evaluated in a 24-week, randomized, double-blind study involving over 700 patients with type 2 diabetes. <sup>(11)</sup> The primary objective of the study was to evaluate the non-inferiority of adding *Avandia* 4 mg twice daily to submaximal doses of metformin (1000 mg/day) relative to up-titrated metformin monotherapy (2000 mg/day) in achieving glycemic control.

Patients enrolled into the study included drug naïve patients as well as patients treated with monotherapy or combination antidiabetic agents. <sup>(11)</sup> After a 2-week washout period, patients received open-label metformin, which was uptitrated to a dose of 1000 mg/day over 4-7 weeks. After the metformin titration period, patients entered a 24-week, double-blind phase and were randomized to receive either *Avandia* 2 mg twice daily plus open-label metformin 1000 mg/day ( $n = 382$ ) or metformin monotherapy (blinded-metformin 500 mg plus open-label metformin 1000 mg) ( $n = 384$ ). At week 8, patients had their blinded medication increased: *Avandia* 2 mg twice daily increased to 4 mg twice daily and metformin 500 mg/day increased to 1000 mg/day.

Baseline demographics were similar between groups. <sup>(11,58)</sup> The majority of patients were male (51%) and white (72%), with a mean age of 56 years and a mean BMI of 34 kg/m<sup>2</sup>.

The primary endpoint was to compare the mean change in HbA1c from baseline to week 24 between groups. <sup>(11)</sup> Secondary endpoints included change in FPG and the percent of patients reaching American Diabetes Association (ADA) and American Association of Clinical Endocrinologists (AACE) HbA1c

goals. Changes in HbA1c and FPG from baseline to Week 24 for the intent-to-treat completer population are provided in Table 13.

**Table 13. Change in HbA1c and FPG (11,58) \***

Parameter	MET 2000 mg/day	<i>Avandia</i> 4 mg BID + MET 1000 mg/day
<b>HbA1c (%)</b>		
n	277	296
Baseline (mean)	7.9	8
Change from baseline (mean)	-0.7	-0.9
Difference from MET (95% CI)	-	-0.2 (-0.36, - 0.04)†
<b>FPG (mmol/L)</b>		
n	237	238
Baseline (mean)	171	181
Change from baseline (mean)	-20	-41
Difference from MET (95% CI)		-15 (-22.1, -8.5)‡
BID = twice daily; FPG = fasting plasma glucose; MET = metformin; RSG = rosiglitazone. *Intent-to-treat completers; † RSG 4 mg BID + MET 1000 mg/day was found to be as effective as MET 2000 mg/day in improving HbA1c; ‡P value vs. MET < 0.0001		

At week 24, the difference in mean HbA1c between groups demonstrated that *Avandia* plus submaximal metformin (1000 mg/day) was as effective as uptitrated metformin (2000 mg/day) monotherapy. <sup>(11)</sup> A greater percentage of patients who received *Avandia* plus submaximal metformin were able to achieve the ADA HbA1c goal of < 7% compared to patients who received uptitrated metformin monotherapy (58% vs. 48%, respectively). Additionally, 41% of patients in the combination group were able to achieve the AACE HbA1c goal of ≤ 6.5% compared to 28% in the uptitrated metformin alone group.

The most commonly reported adverse events (≥ 5%) in patients who received *Avandia* plus sub-maximal metformin included URTI, diarrhea, abdominal pain, dyspepsia, flatulence, and injury.<sup>(58)</sup> Patients treated with *Avandia* plus submaximal metformin reported fewer GI adverse events than those treated with uptitrated metformin monotherapy (28.5% vs. 39.1% , respectively). The odds of experiencing a GI adverse event were 63% greater with uptitrated metformin monotherapy compared to *Avandia* plus submaximal metformin ( $P = 0.0023$ ). <sup>(11)</sup> Fewer patients in the combination group compared to those treated with uptitrated metformin monotherapy discontinued therapy due to GI effects (3.1% vs. 6.8%).

The incidence of edema was 4.7% with *Avandia* plus submaximal metformin vs. 1.3% with uptitrated metformin monotherapy.<sup>(58)</sup> <sup>(11)</sup> The percentage of patients who discontinued due to edema was 0.5% and 0% with *Avandia* plus submaximal metformin and uptitrated metformin monotherapy, respectively. Patients treated with *Avandia* plus submaximal metformin reported more cardiac ischemic adverse events than those treated with uptitrated metformin monotherapy (1.3% vs. 0.8% , respectively). Two patients from the *Avandia* plus submaximal metformin group withdrew due to a myocardial infarction and one in the uptitrated metformin group withdrew due to coronary artery disease.

From baseline to week 24, an increase in mean body weight (+1.79 kg) was observed with *Avandia* plus submaximal metformin ( $n = 297$ ), whereas a decrease in mean body weight (-1.78 kg) was observed with uptitrated metformin monotherapy ( $n = 292$ ). In the combination group, 55% of patients experienced a 0 to < 2 kg increase in weight.<sup>(58)</sup> <sup>(11)</sup>

## 5.2 Use of *Avandamet* as Initial Therapy for the Treatment of Type 2 Diabetes

### Background

*Avandamet* tablets contain two oral antihyperglycemic drugs used in the management of type 2 diabetes: a thiazolidinedione (rosiglitazone maleate) and a biguanide (metformin HCl).<sup>(8)</sup> *Avandamet* is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus when treatment with dual rosiglitazone and metformin therapy is appropriate.



## Clinical Information

### Double-Blind Study

A 32-week, multi-center, randomized, double-blind study (Study 007) evaluated the efficacy and safety of *Avandamet* in 468 drug-naïve subjects (aged 18-70 years) with type 2 diabetes.<sup>(8,9,80)</sup> The primary objective was to demonstrate the superiority of *Avandamet* compared to both rosiglitazone and metformin monotherapies with respect to mean change from baseline in HbA1c after 32 weeks of treatment.

To be eligible for the study, subjects had to be treated with diet and/or exercise alone or had not taken >15 days of an oral anti-diabetic medication or insulin in the past 12 weeks to be considered drug-naïve.<sup>(9)</sup> If a previously drug-naïve subject took ≤15 days of oral anti-diabetic medication or insulin in the past 2 weeks, a wash-out period of at least 2 weeks was to be completed prior to screening. At screening, subjects had to have an HbA1c >7.5% and ≤11.0% and fasting plasma glucose (FPG) ≤270 mg/dL to be eligible for inclusion in the study. Subjects who had HbA1c >11% or FPG >270mg/dL were not eligible for this study, but were eligible for enrollment into a 24-week, open-label companion study with *Avandamet* (Study 004).<sup>(8,10)</sup> Eligible subjects were randomized to one of three treatment regimens:

***Avandamet* Treatment Regimen** - An initial total daily dose of *Avandamet* 2mg/500mg could be increased up to *Avandamet* 8mg/2000mg in increments of 2mg/500mg.

**Rosiglitazone Treatment Regimen** - An initial total daily dose of rosiglitazone 4mg could be increased up to rosiglitazone 8mg.

**Metformin Treatment Regimen** - An initial total daily dose of metformin 500mg could be increased up to metformin 2000mg in increments of 500mg.

Subjects were titrated to the maximum tolerated dose unless the pre-defined glycemia target (mean daily glucose ≤110mg/dL) was achieved.

### Open-Label Study

An open-label, 24-week, single-arm clinical trial evaluated the safety and efficacy of *Avandamet* in 190 poorly-controlled drug-naïve subjects with type 2 diabetes.<sup>(8,10)</sup> Subjects that did not meet eligibility criteria for enrollment in Study 007 due to HbA1c >11% or FPG > 270mg/dL were enrolled provided they met all other inclusion and exclusion criteria. *Avandamet* treatment was initiated with a total daily dose of 4 mg/1000mg. As tolerated, the dose was increased to 6 mg/1500mg at Week 4 and to the maximum dose of 8 mg/2000mg at Week 8.<sup>(81)</sup> Subjects who did not show adequate glycemic lowering were withdrawn for insufficient therapeutic effect if they had been on *Avandamet* 8 mg/2000 mg for at least 4 weeks and the FPG was >240 mg/dL.

Efficacy results for Study 007 (32-week, double blind) are presented in Table 1:

**Table 14. Change in HbA1c and FPG from Baseline to Week 32 in Study 007 (ITT with LOCF)<sup>(8,9,80)</sup>**

Ref	N (ITT)	Regimen	Baseline HbA1c (%) / FPG (mg/dL)	Primary Endpoint HbA1c (%)		Secondary Endpoint FPG (mg/dL)	
				Mean Change From Baseline	Mean Difference From Comparator	Mean Change From Baseline	Mean Difference From Comparator
Study 007	152	<i>Avandamet</i>	8.9/200.7	-2.27	NA	-73.9	NA
	155	Rosiglitazone	8.8/194.0	-1.55	- 0.63*	-47.3	-22.0*
	150	Metformin	8.8/199.0	-1.79	-0.42†	-50.9	-22.0*

\*  $P < 0.0001$ ; †  $P = 0.0008$

ITT = Intent to Treat; LOCF = Last Observation Carried Forward; NA = Not applicable.

The proportion of subjects (Intent-to-treat with Last Observation Carried Forward) with HbA1c <7% was higher in subjects that received *Avandamet* (77%) compared to those who received metformin (57%) and rosiglitazone (58%) monotherapies at Week 32.<sup>(8,9)</sup> Similarly, a higher percentage of subjects that received

*Avandamet* reached HbA1c targets of  $\leq 6.5\%$  (60%) compared to subjects in the metformin (39%) and rosiglitazone (36%) monotherapy groups. Fewer subjects were titrated to the highest dose level with *Avandamet* (8 mg/2000 mg; 74%) compared to metformin (2000 mg; 82%) and rosiglitazone (8 mg; 94%). At study end, the mean final dose was 7.2 mg/1799 mg for *Avandamet*, 1847 mg for metformin, and 7.7 mg for rosiglitazone.<sup>(80)</sup>

For Study 004 (24-week, open-label), an analysis of all enrolled subjects with last observation carried forward, subjects achieved a statistically significant ( $P < 0.0001$ ) reduction in mean A1C of 4% from baseline (Baseline HbA1c: 11.8%) to Week 24.<sup>(8,10)</sup> Additionally, there was a statistically significant reduction from baseline (Baseline FPG: 305 mg/dL) in mean FPG at Week 24 (-139 mg/dL;  $P < 0.0001$ ). A reduction in mean FPG (94 mg/dL) was observed within 4 weeks of initiating treatment. Given the lack of direct comparators in this evaluation, determination of the exact contribution of rosiglitazone and metformin as well as diet and exercise, to the observed improvement in glycemic control is not possible.<sup>(8)</sup> The majority of subjects (162/184, 88%) were titrated to the maximum dose of *Avandamet* 8mg/2000mg.<sup>(81)</sup>

*Avandamet*, as initial therapy, was generally well tolerated. The most commonly reported adverse events in Study 007 (32-weeks, double-blind) were nausea/vomiting, diarrhea, headache and dyspepsia.<sup>(8,9)</sup> Three subjects reported hypoglycemia documented by symptoms and a confirmatory fingerstick blood glucose measurement  $\leq 50$  mg/dL [*Avandamet* (1 subject), metformin (2 subjects) and rosiglitazone (0 subjects)]. No overall change in mean weight was observed in subjects receiving *Avandamet*.<sup>(9)</sup> The median increase in weight from baseline (25th, 75th percentile) was 0.05 kg (-3.45, 3.0), 1.7 kg (-1.2, 4.5) and -2.2 kg (-5.5, -0.5) with *Avandamet*, rosiglitazone monotherapy and metformin monotherapy, respectively. A summary of the safety results are presented in the Table below.

**Table 15. On-Therapy Adverse Events Reported by  $\geq 5\%$  of Subjects in Study 007 (Safety Population)<sup>(8)</sup>**

	<i>Avandamet</i> N = 155	Rosiglitazone N = 159	Metformin N = 154
Preferred Term	%	%	%
Subjects with at least one AE	81	79	73
Nausea/vomiting	16	8	13
Diarrhea	14	7	21
Headache	11	10	12
Dyspepsia	10	9	8
Upper respiratory tract infection	9	8	7
Dizziness	8	5	3
Edema*	6	7	3
Nasopharyngitis	6	4	5
Abdominal pain	5	7	6
Arthralgia	5	7	3
Loose stools	5	1	6
Constipation	5	6	4
Influenza	1	6	2

\* Terms for peripheral edema, generalized edema, and pitting edema were combined.

There were no discontinuations due to hypoglycemia in subjects receiving *Avandamet*.<sup>(8,9)</sup>

Ischemic heart disease was reported in 5 subjects: one in the *Avandamet* group, two in the metformin group and two in the rosiglitazone group.<sup>(9)</sup> Two of these events were reported as serious, but did not lead to withdrawal: angina pectoris in a subject treated with metformin and myocardial infarction in a subject treated with rosiglitazone. Similar rates of edema were reported for the *Avandamet* (6%) and rosiglitazone groups (7%). Edema was reported in 3% of subjects treated with metformin alone. All reports of edema were considered mild or moderate in intensity with one subject in the rosiglitazone group withdrawn because of edema. There were no reports of congestive heart failure.

In Study 004 (24-weeks, open-label) a total of 124 (65%) subjects reported at least one on-therapy adverse event (AE).<sup>(10,81)</sup> The two most commonly reported adverse events were diarrhea (12%) and upper respiratory tract infection (7%). Mean weight increased by 2.6 kg from baseline to Week 24. The mean increase in weight from baseline with *Avandamet* was 2.6 kg.

## 6. ADDITIONAL SAFETY INFORMATION

### 6.1 Interim Analysis of the RECORD Study

#### RECORD

RECORD (*Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycemia in Diabetes*), a long-term, randomized, multicenter, open-label, noninferiority study in type 2 diabetes patients, was initiated by GlaxoSmithKline in 2000.<sup>(55,82)</sup> The study was designed to prospectively compare cardiovascular outcomes in patients with type 2 diabetes treated with *Avandia* plus metformin or sulfonylurea (*Avandia* group) with outcomes in patients treated with metformin plus sulfonylurea (control group).

This study included 4447 type 2 diabetes patients with a HbA1c > 7% and ≤9% despite maximum doses of a sulfonylurea or metformin alone from 338 European and Australian study centers.<sup>(55)</sup> After a 4 week run-in, patients who were already taking a sulfonylurea were randomly assigned to receive the addition of either *Avandia* (n=1103) or metformin (n=1122). Patients who were already taking metformin were randomly assigned to receive the addition of either *Avandia* (n=1117) or a sulfonylurea (n=1105). The starting dose of *Avandia* was 4 mg/day and the starting doses of metformin and sulfonylurea were determined by local practice. Throughout the study, medications were titrated (following 8 weeks of treatment) to achieve a target HbA1c of ≤ 7%. The maximum daily dose of *Avandia* was 8 mg/day and the maximum dose of metformin was 2550 mg/day. The maximum dose of sulfonylurea was 15 mg/day for glyburide, 240 mg/day for gliclazide, and 4 mg/day for glimepiride. If HbA1c remained ≥ 8.5%, a third oral antidiabetic agent was added in the *Avandia* group or insulin was added in the control group. Patients in the control group (metformin plus sulfonylurea) who started insulin did so according to local practice with or without continuing metformin and/or sulfonylurea.<sup>(82)</sup> If patients receiving triple therapy in the *Avandia* group had a HbA1c ≥ 8.5%, the study protocol recommended discontinuation of *Avandia* and initiation of insulin. Patients will be followed for approximately 6 years with an anticipated study completion date of late 2008.

The primary endpoint of the study was cardiovascular (CV) hospitalization or death.<sup>(55)</sup> CV hospitalizations included hospitalization for acute myocardial infarction, congestive heart failure (CHF), stroke, unstable angina, transient ischemic attack, unplanned CV revascularization, amputation of extremities, or any other definite CV reason. CV death included death from CHF, acute myocardial infarction, sudden death, and death caused by acute vascular events such as stroke. Secondary outcomes included all-cause mortality, CHF, combined CV death and/or hospitalization plus microvascular endpoints, all microvascular endpoints, progression of glucose control and need for insulin.<sup>(82)</sup> An interim analysis of the glycemic control outcomes at 18 months has been published for RECORD.<sup>(83)</sup> Safety evaluations included monitoring of changes in physical examination, vital signs, laboratory tests, adverse events, and electrocardiograms.

A meta-analysis published in the *New England Journal of Medicine* raised concern regarding the risk of myocardial infarction and CV death associated with *Avandia*. To provide additional information regarding the CV safety of *Avandia*, an unplanned interim analysis was conducted to evaluate the CV outcomes reported so far in the RECORD study.<sup>(55)</sup> Results of this interim analysis study were published in the *New England Journal of Medicine* on June 5, 2007.

In the RECORD study, there were 2220 patients assigned to receive *Avandia* added to metformin or sulfonylurea (*Avandia* group), and 2227 were assigned to receive a combination of metformin plus a sulfonylurea (control group).<sup>(55)</sup> The protocol excluded some high-risk patients (i.e. those with CHF, hospitalization for CV causes during the previous 3 months, and pending CV intervention). Baseline characteristics were similar between treatment groups. A total of 140 patients in the *Avandia* group and 244 patients in the control group began to receive insulin. Approximately 10% of patients (218 in the *Avandia* group and 223 in the control group) were lost to follow-up. The interim analysis of RECORD had

limited statistical power to detect treatment differences because of the number of patients lost to follow-up, because there was a much lower overall event rate than predicted, and because the mean follow-up was only 3.75 years. Due to the limited power of the interim analysis, a conclusion on the primary endpoint must await the completion of the study.

There was no significant difference between the *Avandia* group and the control group in the adjudicated primary endpoint of CV hospitalization and death. <sup>(55)</sup> A total of 217 patients in the *Avandia* group and 202 patients in the control group experienced the adjudicated primary endpoint (hazard ratio, 1.08; 95% confidence interval [CI], 0.89 to 1.31). After the inclusion of endpoints for an additional 91 patients (50 in the *Avandia* group and 41 in the control group) pending adjudication, the hazard ratio was 1.11 (95% CI, 0.93 to 1.32). Overall, the rate of the primary endpoint (CV hospitalization or death) was low: 3.1% per year for adjudicated plus pending events.

For the secondary endpoints of myocardial infarction, death from CV or any cause (total mortality), or the composite of CV death, myocardial infarction, and stroke, hereafter referred to as major adverse cardiovascular events (MACE), there was no statistically significant differences between the *Avandia* group and the control group. <sup>(55)</sup> See Table 16. At this point, the data do not allow a conclusion on the relative risk of myocardial infarction among the medications studied.

**Table 16. Hazard Ratios for the Risk of MACE, Myocardial Infarction, and Total Mortality<sup>(84)</sup>**

	MACE		Myocardial Infarction*		Total Mortality	
	n (%)	HR (95% CI)	n (%)	HR (95% CI)	n (%)	HR (95% CI)
RSG + SU or MET N = 2220	93 (4.2)	0.97 (0.73, 1.28)	49 (2.2)	1.09 (0.73, 1.63)	74 (3.3)	0.92 (0.67, 1.26)
SU + MET N = 2227	96 (4.3)		45 (2.0)		80 (3.6)	

\* Myocardial infarction or sudden death.  
MACE = major adverse cardiovascular events; HR = hazard ratio; CI = confidence interval; RSG = rosiglitazone; SU = sulfonylurea; MET = metformin

Regarding stroke, a post-study ad hoc analysis indicated no statistically significant differences between the *Avandia* group (n = 2220) and the control group (n = 2227) with regard to rate of events per 100 patient-years (0.35 versus 0.46, respectively). <sup>(84)</sup> The risk of stroke was 24% lower in the *Avandia* group as compared with control (HR 0.76: 0.47-1.23).

Patients in the *Avandia* group had a significantly higher risk of CHF than did patients in the control group, with 38 versus 17 adjudicated events (hazard ratio, 2.24; 95% CI, 1.27 to 3.97). <sup>(55)</sup> The inclusion of events pending adjudication increased the number of events to 47 and 22, respectively (hazard ratio, 2.15; 95% CI, 1.30 to 3.57), resulting in an excess risk of CHF in the *Avandia* group of 3.0 (95% CI, 1.0 to 5.0) per 1000 patient years of follow-up.

In summary, a significant difference between the *Avandia* and control groups was seen only in the secondary outcome of CHF, where more than twice the number of cases were seen in patients treated with *Avandia*. <sup>(55)</sup> An independent data safety monitoring board which monitors unblinded safety data twice annually and monitors outcomes throughout the course of the study, has recommended that the RECORD study continue following the interim analysis.

## 7. COMPARATIVE DATA

### 7.1 Results of the ADOPT Trial

A Diabetes Outcome Progression Trial (ADOPT) was an international, multicenter, randomized, double-blind controlled clinical trial involving 4,360 patients with a median treatment of 4 years. <sup>(53)</sup> ADOPT was conducted to evaluate the durability of glycemic control in recently diagnosed (<3 years) type 2 diabetes patients receiving *Avandia*, metformin, or glyburide monotherapy. The primary outcome was

the time to monotherapy failure, defined as confirmed hyperglycemia when fasting plasma glucose (FPG) > 180 mg/dl on consecutive testing after at least 6 weeks of treatment at the maximal effective or tolerated dose.<sup>(53,85)</sup> The therapeutic goal was a FPG < 140mg/dl. Fasting plasma glucose values used within the study protocol are consistent with treatment guidelines during the period of study enrollment.

A total of 6,676 patients was screened of which 4,351 were randomized to receive either *Avandia* (n = 1456), metformin (n=1454), or glyburide (n = 1441).<sup>(53)</sup> Eligible participants randomized for the trial were between the ages of 30 and 75 years, had an FPG that was between 126-180 mg/dl, and had received no prior pharmacologic treatment for their type 2 diabetes; the disease had previously only been managed with diet and exercise. Of those randomized, the majority of participants were male (57.7%), with a mean age and body mass index (BMI) of 56.9 years and 32.2, respectively. Participants with a history of clinically significant hepatic disease, renal impairment, lactic acidosis, unstable or severe angina, congestive heart failure (CHF) New York Heart Association Class I-IV, or uncontrolled hypertension were excluded from participation in the trial.

A placebo run-in of 4 weeks was followed by a median treatment duration of 4 years (maximum 6 years).<sup>(53,85)</sup> Participants were randomized initially to receive a total daily dose of *Avandia* 4mg, metformin 500mg, or glyburide 2.5mg.<sup>(53)</sup> During the treatment period, up-titration occurred during each study visit if FPG ≥ 140 mg/dl to a maximum daily dose of *Avandia* 8mg, metformin 2g, and glyburide 15mg. Dose reduction was permitted if study medication was not tolerated. Participants who withdrew from the study prior to completion were given the option to enter a non-treatment observational follow-up.

The primary outcome was the time from randomization to monotherapy treatment failure. Treatment failure was defined as:

- Confirmed hyperglycemia (FPG > 180mg/dl) on consecutive testing after at least 6 weeks of treatment at the maximum tolerated or dictated dose.

An independent adjudication committee used criteria to determine whether the primary outcome had been met in cases where a confirmatory FPG had not been obtained, a patient had withdrawn due to insufficient therapeutic effect, or an additional glucose lowering agent had been administered prior to confirmed hyperglycemia.

Secondary outcomes included time from randomization to a confirmed FPG > 140mg/dl after at least 6 weeks of treatment at the maximum tolerated dose of study medication.

Other prespecified secondary outcomes included:

- FPG
- A1C
- Measures of estimates of insulin sensitivity and  $\beta$ -cell function
- Weight

The primary comparisons within the ADOPT trial were *Avandia* versus metformin and *Avandia* versus glyburide. Secondary analysis was conducted to compare metformin and glyburide.

The cumulative incidence of monotherapy failure at 5 years, according to Kaplan-Meier analysis, was 15% with *Avandia*, 21% with metformin, and 34% with glyburide.<sup>(53)</sup> This represents a 32% risk reduction in the primary outcome of time to progression to monotherapy failure with *Avandia* as compared with metformin [95% Confidence Interval (CI) 15-45%;  $P < 0.001$ ], and a 63% risk reduction with *Avandia* as compared with glyburide [95% CI 55-70%;  $P < 0.001$ ]. Additionally, as compared with glyburide, metformin was associated with a 46% risk reduction [95% CI 36-55%,  $P < 0.001$ ] in the primary outcome of time to progression of monotherapy failure. At the time of treatment failure, 99.3 % of participants in the *Avandia* group, 98.6% in the metformin group, and 99.0% in the glyburide group were receiving the maximum dose of study medication. Findings with regard to treatment failure not requiring adjudication remained consistent with those of the primary outcome. A 31% risk reduction in the primary outcome of time to progression to monotherapy failure with *Avandia* as compared with metformin [95% Confidence Interval (CI) 11-46%;  $P = 0.004$ ], and a 66% risk reduction with *Avandia* as compared with glyburide [95% CI 57-73%;  $P < 0.001$ ] was reported for non-adjudicated treatment failures. Subgroup analyses indicated that *Avandia* was more effective than glyburide in all subgroups while a greater treatment effect was seen with

*Avandia* as compared with metformin among older participants ( $\geq 50$  yrs) [ $P$ -value for heterogeneity = 0.03] and those with larger waist circumference ( $>110$ cm) [ $P$ -value for heterogeneity = 0.01].

There was a 36% risk reduction in the secondary outcome of time to progression to FPG  $> 140$ mg/dl with *Avandia* as compared with metformin [79/511 and 127/520, respectively; 95% CI 15-52%;  $P = 0.002$ ] and a 62% risk reduction with *Avandia* as compared with glyburide [79/511 and 160/480, respectively; 95% CI 51-72%;  $P < 0.001$ ]. Additionally, as compared with glyburide, metformin was associated with a 41% risk reduction in time to progression of FPG  $> 140$ mg/dl [95% CI 25-54;  $P < 0.001$ ]. Levels of FPG and A1C decreased in all groups within the first 6 months of treatment, however the annual rate of increase in these glycemic parameters was significantly higher in the metformin and glyburide groups as compared with *Avandia* ( $P < 0.001$ ). A 4-year evaluation identified that significantly more participants receiving *Avandia* (40%) had an A1C  $< 7\%$  as compared with metformin (36%;  $P = 0.03$ ) and glyburide (26%;  $P < 0.001$ ). Mean A1C  $< 7\%$  was maintained for 57 months with *Avandia*, 45 months with metformin, and 33 months with glyburide.

Estimates of insulin sensitivity and  $\beta$ -cell function were calculated using the homeostasis model assessment (HOMA 2). Insulin sensitivity improved to a greater extent with *Avandia* than with metformin after 6 months of treatment. Thereafter, insulin sensitivity improved at similar rates in the two groups. Insulin sensitivity did not change significantly with glyburide at 4 years. There was a significant improvement in insulin sensitivity with *Avandia* as compared with both metformin (12.6%, 95% CI 8.1-17.3;  $P < 0.001$ ) and glyburide (41.2%, 95% CI 35.2-47.4;  $P < 0.001$ ) at 4 years.  $\beta$ -cell function declined in all treatment groups. The annual rate of decline after 6 months of treatment was significantly less with *Avandia* (-2.0%) as compared with metformin (-3.1%;  $P = 0.02$ ) and glyburide (-6.1%;  $P < 0.001$ ). Mean change in body weight from baseline was +4.8 kg with *Avandia*, -2.9 kg with metformin, and +1.6 kg with glyburide.

Cardiovascular events were reported in 4.3% ( $n = 62$ ) receiving *Avandia*, 4.0% ( $n = 58$ ) in the metformin group, and 2.8% ( $n = 41$ ) in the glyburide group and serious cardiovascular events were reported in 3.4% ( $n = 49$ ) receiving *Avandia*, 3.2% ( $n = 46$ ) in the metformin group, and 1.8% ( $n = 26$ ) in the glyburide group ( $P \leq 0.05$  *Avandia* versus glyburide). Additionally, investigator-reported CHF occurred in 1.5% ( $n = 22$ ), 1.3% ( $n = 19$ ), and 0.6% ( $n = 9$ ) of participants receiving *Avandia*, metformin, and glyburide, respectively ( $P \leq 0.05$  *Avandia* vs glyburide) and serious investigator-reported CHF occurred in 0.8% ( $n = 12$ ), 0.8% ( $n = 12$ ), and 0.2% ( $n = 3$ ) of participants receiving *Avandia*, metformin, and glyburide, respectively ( $P \leq 0.05$  *Avandia* vs glyburide). The hazard ratio for CHF with *Avandia* as compared with metformin was 1.22 (95% CI, 0.66-2.26;  $P = 0.52$ ) and compared with glyburide was 2.20 (95% CI 1.01-4.79;  $P = 0.05$ ). Of the 51 possible CHF events identified by independent cardiology review of all serious adverse events, 21 were confirmed through review and involved 9 participants receiving *Avandia*, 8 receiving metformin, and 4 receiving glyburide (with 1 death).

A post-study ad hoc analysis was conducted to evaluate the ischemic cardiovascular safety events in ADOPT.<sup>(86)</sup> Results of this analysis are presented in Table 17. The analysis suggests that the risk of myocardial infarction, cardiovascular death, stroke, major adverse cardiovascular events (MACE), and total mortality in patients exposed to *Avandia* was similar to those exposed to either metformin or sulfonylurea.

**Table 17. Ischemic Cardiovascular Events in ADOPT<sup>(42,86)</sup>**

Endpoint	Treatment	# of Events	HR(95% CI)*
Myocardial ischemia (Adverse events, non-adjudicated)	SU (n = 1441)	82	1.18 (0.88-1.57)
	Metformin (n = 1454)	111	0.99 (0.76-1.30)
	<i>Avandia</i> (n = 1456)	106	
Myocardial infarction or sudden death † ‡ (Serious adverse events, adjudicated)	SU (n = 1441)	15	1.20 (0.62-2.35)
	Metformin (n = 1454)	17	1.21 (0.64-2.32)
	<i>Avandia</i> (n = 1456)	20	
Stroke‡ (Serious adverse events, non-adjudicated)	SU (n = 1441)	12	0.94 (0.43-2.07)
	Metformin (n = 1454)	17	0.77 (0.38-1.59)
	<i>Avandia</i> (n = 1456)	13	
CV death‡ (Serious adverse events, adjudicated)	SU (n = 1441)	12	0.46 (0.17-1.23)
	Metformin (n = 1454)	8	0.79 (0.27-2.27)
	<i>Avandia</i> (n = 1456)	6	
MACE‡ (Serious adverse events, adjudicated MI, sudden death, and CV death, non-adjudicated stroke)	SU (n = 1441)	28	1.11 (0.67-1.82)
	Metformin (n = 1454)	36	1.00 (0.63-1.59)
	<i>Avandia</i> (n = 1456)	35	
Total Mortality‡	SU (n = 1441)	21	0.51 (0.25, 1.04)
	Metformin (n = 1454)	15	0.82 (0.39, 1.76)
	<i>Avandia</i> (n = 1456)	12	

HR = hazard ratio; CI = confidence interval; SU = sulfonylurea; MACE = major adverse cardiovascular event [MACE components include serious adverse events for: CV death, myocardial infarction (definite or unconfirmed) or sudden death, and stroke]

\* Statistically, a hazard ratio of 1 means no difference in risk between the two agents being compared. If the confidence interval for a hazard ratio includes 1.0, there is no statistically significant difference between the rates compared. If the confidence interval for a hazard ratio does not include 1.0, that result is deemed statistically significant. † Myocardial infarction includes events adjudicated as definite or unconfirmed; ‡ Post-study ad hoc analysis

Edema was reported in 14.1% of participants receiving *Avandia*, 7.2% of participants receiving metformin, and 8.5% of participants receiving glyburide ( $P \leq 0.01$  *Avandia* vs glyburide and vs metformin). Gastrointestinal events were less frequently reported with *Avandia* (23%) as compared to metformin (38.3%;  $P \leq 0.01$ ). Hypoglycemia was less frequently reported with *Avandia* (9.8%) than metformin (11.6%) and glyburide (38.7%;  $P \leq 0.01$ ). Mean alanine aminotransferase (ALT) levels decreased significantly in participants receiving *Avandia* as compared with both metformin and glyburide ( $P \leq 0.01$ ). Low-density-lipoprotein (LDL) levels were significantly higher with *Avandia* (104 mg/dl) as compared to both metformin (96.5 mg/dl) and glyburide (99.3 mg/dl;  $P \leq 0.01$ ).

At the time the original article was being published, further examination of the data on adverse events identified an unexpected event not part of the prespecified analysis plan. A note added in proof indicated that there was a higher incidence of fractures in patients receiving *Avandia*. There was a significantly higher incidence of fractures observed in women receiving *Avandia* as compared with either metformin or glyburide (9.3%, 5.1%, and 3.5%, respectively;  $P < 0.01$ ). The number of men with fractures did not differ according to treatment group (4.0% with *Avandia*, 3.4% with metformin, and 3.4% with glyburide).

The frequency of upper limb fractures was significantly higher in women receiving *Avandia* (3.4%) as compared with glyburide (1.5%;  $P < 0.05$ ) while the frequency of lower limb fractures was significantly higher with *Avandia* (5.6%) as compared to both metformin (3.1%;  $P < 0.05$ ) and glyburide (1.3%;  $P < 0.01$ ). Upper limb fractures were reported to involve primarily the humerus and the hand while lower limb fractures involved primarily the foot. The number of women with hip fractures did not differ with *Avandia* and metformin (2 patients receiving *Avandia*, 2 receiving metformin, and none receiving glyburide). Fracture observations are under further evaluation.

## 7.2 The Risk of Myocardial Ischemic Events with *Avandia* Compared to Actos

### Limitations of Observational Studies

Although randomized, controlled trials are generally considered to be the best method of assessing risk, observational studies are often used to address research questions.<sup>(87)</sup> Observational studies are an important source of data to address safety related questions as they evaluate large populations of diverse individuals in a real world setting. However, observational studies can be vulnerable to methodological problems.<sup>(87,88)</sup> When evaluating observational studies, it is important to assess all possible reasons for an association including bias, confounding, chance, as well as cause.<sup>(87)</sup>

Randomized, controlled clinical trials specifically designed to evaluate the differences in the risk of myocardial ischemic events between *Avandia* and pioglitazone have not been conducted.

### Background

Statistically, a hazard ratio (HR) of 1 means no difference in risk between the two agents being compared. If the confidence interval for a HR includes 1.0, there is no statistically significant difference between the rates compared. If the confidence interval for a HR does not include 1.0, that result is deemed statistically significant.

### Pharmetrics Study<sup>(89,90)</sup>

An observational study was commissioned by GSK, which analyzed 402,845 patients with type 2 diabetes, using the PharMetrics Patient-Centric database, including a head-to head comparison of *Avandia* (n = 57,381) to pioglitazone (n = 51, 641). The database consists of automated claims patient data that have been aggregated from over 80 managed care databases in the United States. Between July 2000 and March 2007, new users of specific anti-diabetic regimens were identified and classified into monotherapy with *Avandia*, pioglitazone, metformin, or sulfonylurea, dual therapy with any 2 of these agents, or the use of any of these agents or other oral anti-diabetic drugs in combination with insulin. The primary outcome of the study was the first occurrence of myocardial infarction (MI) or coronary revascularization (CR). Hospital discharge diagnoses from insurance claims were used to identify new cases of MI or CR during follow-up. The average follow-up ranged from 12 to 18 months across the different cohorts. Relative risks for pair wise head-to-head comparisons within monotherapy, dual therapy, and combination with insulin cohorts were calculated using a stratified Cox-proportional hazards model, with 10 strata created from the central 90 percent of the propensity scores appropriate to each pair.

In the monotherapy cohorts, the number of patients receiving *Avandia*, pioglitazone, metformin, and sulfonylureas was 12,440, 16,302, 131,075, and 48,376, respectively. For the composite outcome of MI and/or CR, the hazard ratio (HR) for *Avandia* versus pioglitazone was 0.97 [95% confidence interval (CI): 0.78-1.20], indicating no statistically significant difference between these thiazolidinediones. Additionally, for MI alone, the HR for *Avandia* versus pioglitazone was 0.78 (95% CI: 0.52-1.18).

In the dual therapy cohorts, 36,906 patients were receiving *Avandia* in combination with metformin or sulfonylurea and 27,415 patients were receiving pioglitazone in combination with metformin or sulfonylurea. Outcome rates for the composite of MI and/or CR in patients receiving *Avandia* versus those receiving pioglitazone were similar in combination with both metformin (HR 0.97, 95% CI: 0.81-1.17) and sulfonylureas (HR 1.12, 95% CI: 0.89-1.41). Additionally, for MI alone, the outcome rates in patients receiving *Avandia* versus those receiving pioglitazone were similar in combination with both metformin (HR 1.01, 95% CI: 0.71-1.44) and sulfonylureas (HR 1.22, 95% CI: 0.83-1.78).



In the combination-with-insulin cohorts, 8,035 and 7,924 patients were receiving *Avandia* and pioglitazone, respectively. In these two groups, the risk of the composite outcome of MI and/or CR and MI alone were similar (HR 1.07 95% CI: 0.89-1.29 and HR 1.02 95% CI: 0.75-1.39, respectively).

The overall hazard ratios for the composite outcome of MI and/or CR and its individual components of MI or CR comparing all *Avandia* regimens to all pioglitazone regimens are provided in Table 18. The risk of MI, CR, and the composite outcome of MI and CR was similar between *Avandia* and pioglitazone.

**Table 18. Hazard Ratio of Composite and Individual Outcomes: *Avandia* regimens vs. Pioglitazone regimens<sup>(90)</sup>**

	HR	95% CI
MI	1.07	0.89-1.27
CR	1.03	0.93-1.14
Composite outcome: MI and CR	1.04	0.94-1.14

MI = myocardial infarction; CR = coronary revascularization; HR = hazard ratio; CI = confidence interval

There are several limitations with regard to this analysis. In considering crude incidence rates, it is important to note that sulfonylurea initiators were generally older compared to metformin initiators, which included a relative preponderance of subjects under the age of 35. These younger patients also had fewer comorbid conditions and baseline cardiovascular risk factors. Initiators of *Avandia* and pioglitazone were more similar to one another in patient characteristics than patients on other regimens. Pioglitazone initiators had a higher prevalence of baseline hyperlipidemia than did *Avandia* initiators (48.3% for pioglitazone monotherapy compared to 42.5% for *Avandia* monotherapy). However, this difference was adjusted by including hyperlipidemia in the propensity score.

#### **Ingenix Study<sup>(91)</sup>**

A retrospective cohort study was conducted by Takeda Pharmaceutical Company Limited using the Ingenix database to analyze patients who initiated *Avandia* or pioglitazone between 2003-2006. The objective of this study was to compare the risk of hospitalization for acute MI in type 2 diabetes patients treated with pioglitazone relative to *Avandia*. The primary and secondary outcomes of hospitalization for acute MI, and composite of acute MI or CR were evaluated using hospital discharge diagnosis ICD-9 coding. The HR of incident hospitalization for acute MI and for the composite endpoint of acute MI or CR, in patients using pioglitazone compared to *Avandia* was estimated from multivariate Cox's proportional hazards survival analysis. Several baseline variables were considered potential risk factors for MI and were introduced into the statistical model as covariates including: age, gender, duration of diabetes drug treatment, year of index drug initiation, medical conditions and procedures such as hypertension, prior MI, prior CR, angina, unstable angina, coronary heart disease, congestive heart failure, hyperlipidemia, smoking, obesity, arrhythmias, and stroke, and dispensed drugs including metformin, sulfonylurea, meglitinides, insulin, other anti-diabetic agents, nitrates, beta-blockers, calcium-channel blockers, diuretics, angiotensin-converting enzyme (ACE)-inhibitors, angiotensin-receptor blockers, statins, fibrates, aspirin, non-steroidal antiinflammatory drugs, antiplatelet agents, and anticoagulants.

In total, 29,911 patients were included in the study with 14,807 in the pioglitazone group and 15,104 in the *Avandia* group. The groups were generally well balanced at baseline; however, the use of statins and fibrates was higher in patients receiving pioglitazone as compared with *Avandia* (statins: 39.9% vs. 34.7% and fibrates: 10.1% vs. 8.0%). Additionally, more patients in the *Avandia* group were receiving metformin (55.2% vs. 41.6%) as compared to pioglitazone. In the pioglitazone and *Avandia* groups, the average follow-up time was 1.2 years and 1.3 years, respectively.

In the group receiving pioglitazone, 161 (1.1%) patients were hospitalized for acute MI, which constitutes an unadjusted incidence rate of 93.3 (95% CI: 80.0-108.8) per 10,000 patient-years. In the *Avandia* group, 214 (1.4%) patients were hospitalized for acute MI, constituting an unadjusted incidence rate of 111.3 (95% CI: 97.0-127.1) per 10,000 patient years. The unadjusted HR for hospitalization for acute MI for pioglitazone relative to *Avandia* was 0.82 (95% CI: 0.67-1.01), indicating no statistically significant difference between the groups, and 0.78 (95% CI: 0.63-0.96) after adjusting for the baseline covariates described above. There were 386 (2.6%) patients in the pioglitazone group and 468 (3.1%) in the *Avandia* group with a first event in the composite endpoint of acute MI or CR. The adjusted HR was 0.85 (95% CI: 0.75-0.98).

To assess the differences in baseline use of metformin and lipid lowering agents, sensitivity analyses were conducted. The HR for patients in the pioglitazone group relative to the *Avandia* group who were receiving metformin at baseline was 0.85 (95% CI: 0.62-1.19), while the HR was 0.74 (95% CI: 0.56-0.97) for those who were not receiving metformin. Among patients who were receiving statins or fibrates at baseline, the HR for acute MI was 0.59 (95% CI: 0.43-0.81). However, among patients who were not taking these agents at baseline, there was no difference in acute MI between the pioglitazone and *Avandia* groups [HR 0.96 (95% CI: 0.73-1.26)].

Several aspects of this study create potential bias. The use of lipid lowering agents is known to help reduce the risk of MI, and in this study, the use of statins and fibrates was higher in the pioglitazone group compared to the *Avandia* group. In addition, the study does not distinguish between results for patients taking pioglitazone and *Avandia* as monotherapy, dual therapy, and combinations with insulin. Therefore, the mix of therapies was unknown between the groups. Patients on combination therapy may have more progressive disease and may be at a greater risk of events. A difference in the distribution of monotherapy, dual therapy, and combination therapy with insulin between the groups may have contributed to the difference in outcomes between pioglitazone and *Avandia*.

### Wellpoint Cohort Study

A retrospective-longitudinal cohort study was conducted by HealthCore, the health outcomes research subsidiary of WellPoint.<sup>(92)</sup> WellPoint is a health benefits company providing health coverage to over 34 million Americans. This study was entirely funded by WellPoint and conducted to determine if there is evidence in a real world setting of elevated risk of myocardial infarction (MI) in patients receiving *Avandia* or pioglitazone. The primary objective was to determine the risk of acute MI in patients taking *Avandia* or pioglitazone compared to patients taking other oral antidiabetic agents (OADs). Details of this study are limited to what was presented at the Joint Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee on July 30, 2007.

The study used integrated health claims data including pharmacy, medical, and member eligibility for five of WellPoint's plans from January 1, 2001 through December 31, 2006. The *Avandia* cohort included patients taking *Avandia* as monotherapy or in combination with other OADs. Similarly, the pioglitazone cohort included patients taking pioglitazone as monotherapy or in combination with other OADs. Subjects taking insulin or both TZD's during the evaluation period were excluded. Acute MI was determined by review of all medical claims for care in the hospital or emergency room using ICD-9 codes (410.XX). As part of the sensitivity analysis, the definition of acute MI was expanded to include unstable angina (ICD-9 code 411.1X). The severity of illness, complications and intensity of diabetes were determined by evaluation of covariates including markers of cardiovascular (CV) risk in the year prior to initiating therapy.

Multivariate Cox-proportional hazards modeling was used to evaluate the independent effects of exposure to *Avandia*, pioglitazone, and other OADs on the risk of acute MI. Baseline CV risk factors were adjusted for using the CV risk score. In addition, extensive sensitivity analyses were conducted to assess the impact of definition of outcome and exposures.

The study sample included 22,050 users of *Avandia*, 23,768 users of pioglitazone, and 120,771 users of other OADs. Patients taking *Avandia* and pioglitazone were significantly older and had a higher burden of comorbidities than patients taking all other OADs. Patients taking *Avandia* and pioglitazone had a significantly higher pre-index CV disease and CV medication utilization. A statistically significant greater use of angiotensin-receptor blockers, beta-blockers, calcium-channel blockers and lipid-altering medications was observed in the pioglitazone cohort compared to the *Avandia* cohort ( $P < 0.05$  for each medication). Both *Avandia* and pioglitazone patients had almost twice the diabetic hospitalizations and a greater burden of complications including retinopathy and nephropathy compared to patients treated with OADs prior to treatment.

The number of incident acute MIs excluding angina was 212 for *Avandia*, 232 for pioglitazone, and 866 for other OADs. The incidence rates of acute MI were 0.73, 0.74, and 0.72 per 100 patient years for *Avandia*, pioglitazone, and other OADs, respectively. When angina was included, the incidence rates were 1.43, 1.33, and 1.34 per 100 patient years, respectively as above. The adjusted hazard ratio (HR) for acute MI for patients treated with *Avandia* compared to other OADs was 1.029 ( $P = 0.710$ ) and 1.044 ( $P = 0.553$ ) in patients treated with pioglitazone (Table 19).

**Table 19. Adjusted Hazard Ratios of Acute MI including and Excluding Unstable Angina for Avandia, Pioglitazone and Other OADs<sup>(92)</sup>**

	Acute MI = 410.XX (ICD-9 code)			Acute MI = 410.XX or 411.1X		
	HR	95% CI	P- value	HR	95% CI	P- value
<i>Avandia</i>	1.029	0.886-1.194	0.710	1.086	0.979-1.205	0.117
Pioglitazone	1.044	0.905-1.205	0.553	0.987	0.890-1.095	0.808
OADs	reference	reference	reference	reference	reference	reference

CI = Confidence interval; HR = Hazard ratio; MI = Myocardial infarction; OADs = Oral antidiabetic agents

Compared to oral antidiabetic agents, the adjusted HR for acute MI excluding angina for monotherapy cohorts (almost 6,000 for *Avandia* and 9,000 for pioglitazone) was 0.977 in patients taking *Avandia* and 0.861 in patients taking pioglitazone, neither one was statistically significant (Table 20).

**Table 20. Adjusted Hazards Ratios of Acute MI including and Excluding Unstable Angina in Monotherapy Cohorts for Avandia, Pioglitazone, and Other Oral Antidiabetic Agents<sup>(92)</sup>**

	Acute MI = 410.XX (ICD-9 code)			Acute MI = 410.XX or 411.1X		
	HR	95% CI	P- value	HR	95% CI	P-value
<i>Avandia</i>	0.977	0.734 – 1.301	0.874	1.159	0.963 – 1.395	0.118
Pioglitazone	0.861	0.610 – 1.216	0.396	0.912	0.720 - 1.155	0.445
Other OADs	reference	reference	reference	reference	reference	reference

CI = Confidence interval; HR = Hazard ratio; MI = Myocardial infarction; OADs = Oral antidiabetic agents

When the analysis was limited to that of drug treatment period, the HR for acute MI was 0.945 for *Avandia* and 0.90 for pioglitazone with no statistical significance (Table 21).

**Table 21. Adjusted HR of Acute MI Including and Excluding Unstable Angina for Avandia, Pioglitazone, and Other Oral Antidiabetic Agents Limited to Treatment Period<sup>(92)</sup>**

	Acute MI = 410.XX (ICD-9 code)			Acute MI = 410.XX or 411.1X		
	HR	95% CI	P- value	HR	95% CI	P-value
<i>Avandia</i>	0.945	0.656 – 1.362	0.762	0.959	0.764 – 1.203	0.718
Pioglitazone	0.900	0.633 – 1.278	0.555	0.811	0.646 - 1.020	0.073
Other OADs	reference	reference	reference	reference	reference	reference

CI = Confidence interval; HR = Hazard ratio; MI = Myocardial infarction; OADs = Oral antidiabetic agents

The WellPoint investigators reported that they did not identify a statistically significant increase in the risk for acute cardiac events, including MI and unstable angina, in patients who received *Avandia* or pioglitazone when compared to patients taking other oral anti-diabetic agents.<sup>(92)</sup> In addition, a sub-cohort of patients treated with *Avandia* or pioglitazone as monotherapy were also found to not have an elevated risk of acute cardiac events.

### Tricare Study<sup>(93,94)</sup>

The Department of Defense conducted a cross-sectional analysis of data from fiscal years 2003-2006 to determine if there was an increased incidence of acute MI and CHF among Military Health System (MHS) beneficiaries who filled a prescription for *Avandia* compared to those who filled a prescription for other antidiabetic medications. The MHS provides health coverage to approximately 9.1 million beneficiaries. The data for the analysis was collected from enrollees of TRICARE Prime, which is a managed care option similar to a civilian health maintenance organization. The study was limited to individuals younger than 65 years of age since older individuals are not eligible for TRICARE Prime. This information was presented at the Joint Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee on July 30, 2007 and recently published in the *American Journal of Therapeutics*.

The analysis used three different data sources: Defense Eligibility Enrollment System (DEERS), inpatient/outpatient encounter claims, and Pharmacy Data Transaction Service (PDTS). DEERS provided data necessary for the establishment of demographic characteristics of the population. The inpatient/outpatient encounter claims included the date and source of service received, diagnoses of diseases according to ICD-9 and procedure codes (DRG). PDTS allowed tracking of the real time prescription fill records regardless of sources of fill. The three data sources were linked by identifiers.

Type 2 diabetes was defined using the ICD-9 code. Individual drugs were grouped into therapeutic classes of antidiabetic drugs. The drug categories defined were not mutually exclusive, and therefore, statistical comparisons of the drugs analyzed were not preformed. Incident cases of acute MI and CHF were identified using the earliest date of diagnosis.

In total, 231,962 diabetic patients were included in the study of which 46% were male and 54% were female. Approximately 70% of the individuals in the study were between 45 and 64 years of age. Table 22 provides the annual incidence rates of acute MI averaged over the 4 year period of the study.

**Table 22. Annual Incidence Rates of Acute Myocardial Infarction Averaged Over the 4 Year Period in TRICARE Prime (2003-2006) <sup>(93,94)</sup>**

	N Dispensed Drug	Acute MI	
		N	Average Annual Incidence per 10,000
Any TZD	20,002	299	37.37
<i>Avandia</i>	13,400	202	37.69
Pioglitazone	7,831	111	35.44
Biguanides	58,091	769	33.09
Sulfonylureas	23,520	457	48.58
Insulin	11,854	245	51.67
Nitrates	6561	831	316.64
<i>Avandia</i> + nitrates	1320	177	335.23
Pioglitazone + nitrates	891	131	367.56

The authors concluded that there was no increased annual incidence of acute MI among TRICARE Prime beneficiaries with a diagnosis of type 2 diabetes who have filled a prescription for *Avandia* compared with those who filled prescriptions for other antidiabetic medications.

There were several limitations to this study. The study did not adjust for potential confounding factors such as socioeconomic status, comorbid conditions, current health status, medical history, drug dose, time on drug, concurrent medications, or individual characteristics such as body mass index, diet, smoking, and exercise. Therefore, it was not possible to determine whether the observed differences in average annual incidence rates of the outcomes were due to the inherent differences in antidiabetic drugs or other confounding factors such as disease progression, other risk factors for cardiovascular events such as age, and the differences in the number, type, and severity of comorbid conditions. The study also did not include individuals who were 65 years of age and older. The outcome of acute MI was attributed to the antidiabetic class if the prescription was filled at any time prior to the event, assuming a cause-effect relationship. An additional limitation was that the drug categories were not mutually exclusive and therefore statistical comparisons for significance were not possible.

### **Integrated Healthcare Information Services (IHCIS) Study<sup>(95,96)</sup>**

An observational study was conducted using the Integrated Healthcare Information Services (IHCIS) database, a U.S. managed care claims database which contains data on 891,901 patients with type 2 diabetes. The study was a case-control analysis nested within the cohort of eligible type 2 diabetic patients captured in IHCIS from 1999-2006. The study was designed to determine the odds of MI in patients with type 2 diabetes exposed to thiazolidinediones (TZDs) (*Avandia* and pioglitazone, separately) compared to those exposed to other anti-diabetic agents. Incident cases of hospitalization for MI were identified among type 2 diabetic patients. Three controls were matched to each case based on age (+/- 5 years), gender, calendar year of diabetes diagnosis, and year of MI diagnosis (index year). The odds of MI were modeled using conditional logistic regression, adjusting for age, gender, ACE-inhibitor use, beta-blocker use, diuretic use, nitrate use, and hyperlipidemia and hypertension diagnosis.

The incidence rate of MI in the diabetic cohort was 5.25 per 1,000 person-years (95% CI: 5.15-5.36). The average follow-up was 2.1 years, during which 9,870 MI cases (1.1%) were identified and matched to 29,610 controls. In the 3 months prior to the index date (recent exposure), 1,149 (11.6%) cases and 2,690 (9.1%) controls were exposed to *Avandia*, 910 (9.2%) cases and 2,433 (8.2%) controls were exposed to pioglitazone, and 5,644 (57.2%) cases and 13,702 (46.3%) controls were treated with other anti-diabetic therapies excluding TZDs. The risk of MI in patients exposed to either *Avandia* or pioglitazone compared

with those patients exposed to other anti-diabetic therapies was 1.03 (95% CI: 0.99-1.12) and 0.92 (95% CI: 0.83-1.01), respectively. The risk of MI in subjects exposed to *Avandia* or pioglitazone for  $\leq 12$  months is not different from those exposed to other antidiabetic agents but exposure for  $>12$  months is associated with a 15% and 13% increased risk of MI, respectively.

A limitation to this analysis is the utilization of a nested-case control study design. Results of cohort studies utilizing propensity scores represent a higher level of study design and evidence.

#### **Institute for Clinical Evaluative Sciences (ICES) Study<sup>(97)</sup>**

A population-based, retrospective nested case-control cohort study was conducted using health care databases from Ontario, Canada to evaluate the risks of congestive heart failure (CHF), acute MI, and all-cause mortality associated with the use of TZDs compared to other oral hypoglycemic drug combination therapies. Of note, reimbursement for TZDs during the time of the study was restricted to patients experiencing uncontrolled hyperglycemia or to those who had a contraindication or intolerance to metformin and/or sulfonylureas. The study population included diabetic patients from Ontario who were 66 years of age or older treated with at least 1 oral hypoglycemic drug between April 1, 2002 and March 31, 2005. Patients who were treated with insulin in the year prior to cohort entry were excluded, while patients who began treatment with insulin during follow-up were retained in the study. Patients were followed up until they experienced an event, death, a last health services contact in Ontario (for those who lost health contact for at least 6 months), or March 31, 2006, whichever occurred first. The primary outcome of the study was a first hospital visit for CHF defined as an emergency room visit for CHF or a hospital admission with CHF as the discharge diagnosis. The secondary study outcomes were a hospital visit for acute MI, defined as either an emergency room visit for MI or a hospital admission with MI as the discharge diagnosis, and all-cause mortality.

The study population consisted of 159,026 diabetic patients who were treated with oral hypoglycemic agents. The mean age of the individuals included in the study was 74.7 years, and the median follow-up for the study was 3.8 years. A greater proportion of patients taking TZD monotherapy had a history of renal and cardiovascular disease compared with those receiving TZD combination therapy and other oral antidiabetic agent combination therapy. Patients receiving *Avandia* monotherapy had greater comorbidity compared with those prescribed pioglitazone monotherapy, although the proportion with a history of cardiovascular disease was similar. All other baseline characteristics were similar between the groups. Cases and controls were well matched for age, sex, cardiovascular history, and duration of diabetes; however, the occurrence of noncardiac comorbidity was somewhat higher among cases than controls.

Overall, 7.9% of patients ( $n = 12,491$ ) had a hospital visit for CHF, 7.9% for acute MI ( $n = 12,578$ ), and 19% died ( $n = 30,265$ ). Compared with patients receiving other oral hypoglycemic agent combination therapy, current users of TZD monotherapy and combination therapy were at an increased risk of CHF and death. An increased risk of acute MI was seen with current use of TZD monotherapy, but not TZD combination therapy, compared to use of other oral hypoglycemic agent combinations. The association between CHF, acute MI, and mortality and TZD therapy appeared to be limited to treatment with *Avandia*; however, there was limited power to explore the association between outcomes and the use of pioglitazone due to the smaller number of patients taking pioglitazone. Table 23 summarizes the results for acute MI and mortality.

**Table 23. Rate Ratios of Acute Myocardial Infarction and All-Cause Mortality With the Use of Thiazolidinediones Compared to Other Oral Hypoglycemic Agent Combination Therapies<sup>(97)</sup>**

	Number of Cases	Number of Controls	Unadjusted Rate Ratio (95% Confidence Interval)*	Adjusted Rate Ratio (95% Confidence Interval)*†	P Value for Adjusted Rate Ratio
<b>Acute Myocardial Infarction</b>					
Current Other OHA Combination Therapy‡	3695	18351			
Current TZD monotherapy§	65	228	1.42 (1.08-1.88)	1.40 (1.05-1.86)	0.02
<i>Avandia</i>	53	147	1.80 (1.31-2.46)	1.76 (1.27-2.44)	<0.001
Pioglitazone	12	81	0.74 (0.41-1.37)	0.73 (0.40-1.36)	0.33
Current TZD Combination Therapy	404	2109	0.96 (0.86-1.07)	0.96 (0.85-1.08)	0.49
<i>Avandia</i>	282	1404	1.00 (0.88-1.15)	1.00 (0.87-1.16)	0.96
Pioglitazone	122	705	0.87 (0.72-1.06)	0.87 (0.71-1.06)	0.17
Past Treatment with TZDs	140	630	1.11 (0.92-1.34)	1.05 (0.87-1.28)	0.62
<i>Avandia</i>	95	424	1.12 (0.90-1.41)	1.06 (0.84-1.34)	0.65
Pioglitazone	45	206	1.10 (0.79-1.52)	1.04 (0.75-1.45)	0.81
<b>All-Cause Mortality</b>					
Current Other OHA Combination Therapy‡	5529	18835			
<p>OHA - Oral hypoglycemic agent; TZD - Thiazolidinedione</p> <p>*All models were also adjusted for current insulin combination therapy (cases = 370; controls = 1084), insulin monotherapy (cases = 361; controls = 1010), other OHA monotherapy (cases = 7667; controls = 40108), and no current therapy (cases = 1803; controls = 8400).</p> <p>†Adjusted for income quintile; residence in long-term care facility; Charlson comorbidity score category; history of use of angiotensin-converting enzyme inhibitors, nonsteroidal anti-inflammatory drugs, <math>\beta</math>-blockers, calcium channel blockers, diuretics, spironolactone, statins, and digoxin; prior metformin use; prior sulfonylurea use; prior use of other OHAs; prior use of TZDs; congestive heart failure in past year and in past 1-5 years; angina in past year and in past 1-5 years; coronary artery bypass graft surgery in past year and in past 1-5 years; coronary catheterization in past year and in past 1-5 years; percutaneous transluminal coronary angioplasty in past year and in past 1-5 years; history of renal disease; and number of drugs prescribed in prior 6 months.</p> <p>‡Other than TZDs; more than 97% were receiving metformin + sulfonylurea.</p> <p>§Current users are those who were dispensed the drug with the days supplied overlapping the index date by 14 days or more.</p> <p>   Past users are those who were dispensed the drug with the days supplied ending between 15 and 365 days before the index date.</p>					

	Number of Cases	Number of Controls	Unadjusted Rate Ratio (95% Confidence Interval)*	Adjusted Rate Ratio (95% Confidence Interval)*†	P Value for Adjusted Rate Ratio
Current TZD monotherapy§	102	392	0.85 (0.68-1.06)	1.29 (1.02-1.62)	0.03
<i>Avandia</i>	76	255	0.99 (0.76-1.29)	1.47 (1.12-1.93)	0.005
Pioglitazone	26	137	0.60 (0.39-0.91)	0.94 (0.61-1.45)	0.78
Current TZD Combination Therapy	497	1440	1.17 (1.05-1.30)	1.24 (1.11-1.39)	<0.001
<i>Avandia</i>	358	1027	1.18 (1.04-1.34)	1.26 (1.10-1.44)	<0.001
Pioglitazone	139	413	1.15 (0.94-1.40)	1.20 (0.98-1.47)	0.08
Past Treatment with TZDs	458	807	1.93 (1.71-2.18)	2.08 (1.82-2.37)	<0.001
<i>Avandia</i>	314	576	1.85 (1.61-2.14)	1.98 (1.70-2.31)	<0.001
Pioglitazone	144	231	2.14 (1.73-2.65)	2.32 (1.85-2.90)	<0.001

OHA - Oral hypoglycemic agent; TZD - Thiazolidinedione

\*All models were also adjusted for current insulin combination therapy (cases = 370; controls = 1084), insulin monotherapy (cases = 361; controls = 1010), other OHA monotherapy (cases = 7667; controls = 40108), and no current therapy (cases = 1803; controls = 8400).

†Adjusted for income quintile; residence in long-term care facility; Charlson comorbidity score category; history of use of angiotensin-converting enzyme inhibitors, nonsteroidal anti-inflammatory drugs,  $\beta$ -blockers, calcium channel blockers, diuretics, spironolactone, statins, and digoxin; prior metformin use; prior sulfonylurea use; prior use of other OHAs; prior use of TZDs; congestive heart failure in past year and in past 1-5 years; angina in past year and in past 1-5 years; coronary artery bypass graft surgery in past year and in past 1-5 years; coronary catheterization in past year and in past 1-5 years; percutaneous transluminal coronary angioplasty in past year and in past 1-5 years; history of renal disease; and number of drugs prescribed in prior 6 months.

‡Other than TZDs; more than 97% were receiving metformin + sulfonylurea.

§Current users are those who were dispensed the drug with the days supplied overlapping the index date by 14 days or more.

|| Past users are those who were dispensed the drug with the days supplied ending between 15 and 365 days before the index date.

This study contains significant limitations which could have biased the results. The database used in this study is composed of a select group of patients. During the study, TZDs were restricted to those patients who failed treatment on metformin and sulfonylurea or for whom sulfonylurea or metformin were contraindicated. Therefore, TZD patients had a higher baseline risk for cardiovascular disease, and the use of TZDs in this database does not reflect the real world use. Patients who were prescribed *Avandia* monotherapy suffered from more chronic diseases compared with those prescribed pioglitazone monotherapy, and therefore, were sicker patients. This difference is not corrected for in the analysis of the data and in the study conclusions. In addition, the TZD monotherapy group had a 3 to 4-fold higher rate of renal impairment, which is indicative of patients with more progressive type 2 diabetes. Furthermore, the authors state that the study may have been underpowered to detect adverse effects associated with pioglitazone due to the relatively small number of patients prescribed this agent. It is stated that larger studies are needed to better determine the relative effect of each agent on cardiovascular outcomes.

### An Inappropriate Comparison Between Meta-analyses

Two meta-analyses were published side by side in the September 12, 2007 edition of the Journal of the American Medical Association (JAMA). One meta-analysis conducted by Singh, et al, assessed the long-term risk of cardiovascular events with *Avandia*, utilizing the endpoints of myocardial infarction, heart failure, and cardiovascular mortality.<sup>(98)</sup> In this analysis the relative risk (RR) for MI for *Avandia* (n = 94/6421) compared to control (n = 83/7870) was 1.42 (95% CI: 1.06-1.91; *P* = 0.02). The RR of heart failure with *Avandia* (n = 102/6421) compared to control (n = 62/7870) was 2.09 (95% CI: 1.52-2.88; *P* < 0.001). There was no significant risk of cardiovascular mortality with *Avandia* (n = 59/6421) compared to control (n = 72/7870) (RR 0.90; 95% CI: 0.63-1.26; *P* = 0.53). The other meta-analysis conducted by Lincoff et al, evaluated a composite endpoint of death, myocardial infarction, or stroke in patients treated with pioglitazone.<sup>(99)</sup> The composite endpoint occurred in 4.4% (n = 375/8554) of patients receiving pioglitazone and 5.7% (n = 450/7836) of patients receiving control therapy (HR 0.82; 95% CI: 0.72-0.94; *P* = 0.005).

These articles appear to be written and published in a manner meant to draw comparisons between *Avandia* and pioglitazone that cannot be made for many reasons, including:

- Each meta-analysis used a set of clinical trials that studied different populations, some studying drug-naïve patients, while others studied patients on insulin or with documented histories of cardiovascular events
- The endpoints used in each of the trials, and each of the meta-analyses were different
- The duration, event rate, analysis method, and event definitions varied across trials

The pioglitazone meta-analysis is based on a small number of studies (19), and is heavily influenced by data from the PROactive study (5,238 patients) which contributed 32% of the entire population of the meta-analysis and 55% of the patient-years.<sup>(99)</sup> PROactive compared diabetic patients who were randomly assigned to pioglitazone or placebo in addition to their existing antidiabetic medications.<sup>(100)</sup>

No statistical difference between *Avandia* and comparators was observed when the endpoint of CV death, myocardial infarction and stroke are applied to the data on *Avandia*, across long-term clinical trials (HR 1.03).<sup>(101)</sup> In RECORD, a study specifically designed to look at cardiovascular events, no appreciable difference was seen between *Avandia* and comparators (HR 0.96).<sup>(55)</sup> These results are similar to the results from the meta-analysis conducted by Lincoff et al, which observed HR 0.82 in patients treated with pioglitazone.<sup>(99)</sup>

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with *Avandia* or any other oral antidiabetic drug.<sup>(42)</sup>

## 8. OTHER STUDIED USES

### 8.1 *Avandamet* and Polycystic Ovary Syndrome (PCOS)

#### Background

Polycystic Ovary Syndrome (PCOS) is an endocrinologic disorder of premenopausal women characterized by hyperandrogenism and chronic anovulation. <sup>(102)</sup> PCOS affects 5-10% of women of childbearing age and is the most common cause of female infertility in the United States. <sup>(103)</sup> <sup>(104)</sup> The most common presenting complaints of women with PCOS are menstrual irregularity and hirsutism. PCOS is associated with significant insulin resistance and with defects in insulin secretion. The insulin-like growth factor (IGF) axis is involved in the pathogenesis of hyperandrogenism. <sup>(105)</sup> IGF-1 is important in the regulation of ovarian follicular maturation and steroidogenesis and is increased in patients with adrenal hyperandrogenism. The insulin-like growth factor binding protein-1 (IGFBP-1) regulates IGF-1 bioavailability in tissues. <sup>(106)</sup> The insulin-like growth factor binding protein-3 (IGFBP-3) binds most circulating IGF-1 and decreased levels of IGFBP-3 appear to be an endocrinologic feature of PCOS. Strategies for the treatment of infertility associated with PCOS have included medications such as clomiphene citrate, metformin, and thiazolidinediones (TZDs). <sup>(104)</sup> <sup>(107)</sup>

#### Clinical Data



Baillargeon et al presented data from a randomized, double-blind, controlled study to evaluate the effect of rosiglitazone and metformin in nonobese, women with polycystic ovary syndrome (PCOS) and normal indices of insulin sensitivity (n = 100).<sup>(108)</sup> Patients were treated with either rosiglitazone 4 mg twice daily, metformin 850 mg twice daily, a combination of rosiglitazone and metformin, or placebo for 6 months. Frequency of ovulation was higher after treatment with insulin-sensitizing drugs. Ovulations per subject in six months were 3.3 in the metformin group, 2.4 in the rosiglitazone group, and 3.4 in the combination group. Ovulation rates increased significantly more with metformin, alone and in combination, than with rosiglitazone. Serum testosterone levels decreased significantly compared to placebo in all treatment groups. Rosiglitazone therapy was associated with mild weight gain (1.1 kg). Please note that neither metformin, rosiglitazone or the combination are FDA-approved for the treatment of PCOS.

## **8.2 Effect of *Avandamet* on Lipids in Drug-Naïve Patients with Type 2 Diabetes**

### **Clinical Information**

#### **Double-Blind Study**

A 32-week, multi-center, randomized, double-blind study (Study 007) evaluated the efficacy and safety of *Avandamet* in 468 drug-naïve subjects (aged 18-70 years) with type 2 diabetes.<sup>(8,9,80)</sup> The primary objective was to demonstrate the superiority of *Avandamet* compared to both rosiglitazone and metformin monotherapies with respect to mean change from baseline in HbA1c after 32 weeks of treatment.

To be eligible for the study, subjects had to be treated with diet and/or exercise alone or had not taken >15 days of an oral anti-diabetic medication or insulin in the past 12 weeks to be considered drug-naïve.<sup>(9)</sup> If a previously drug-naïve subject took ≤15 days of oral anti-diabetic medication or insulin in the past 2 weeks, a wash-out period of at least 2 weeks was to be completed prior to screening. At screening, subjects had to have an HbA1c >7.5% and ≤11.0% and fasting plasma glucose (FPG) ≤270 mg/dL to be eligible for inclusion in the study. Subjects who had HbA1c >11% or FPG >270mg/dL were not eligible for this study, but were eligible for enrollment into a 24-week, open-label companion study with *Avandamet* (Study 004).<sup>(8,10)</sup> Eligible subjects were randomized to one of three treatment regimens:

***Avandamet* Treatment Regimen** - An initial total daily dose of *Avandamet* 2mg/500mg could be increased up to *Avandamet* 8mg/2000mg in increments of 2mg/500mg.

**Rosiglitazone Treatment Regimen** - An initial total daily dose of rosiglitazone 4mg could be increased up to rosiglitazone 8mg.

**Metformin Treatment Regimen** - An initial total daily dose of metformin 500mg could be increased up to metformin 2000mg in increments of 500mg.

Subjects were titrated to the maximum tolerated dose unless the pre-defined glycemia target (mean daily glucose ≤110mg/dL) was achieved.

#### **Open-Label Study**

An open-label, 24-week, single-arm clinical trial evaluated the safety and efficacy of *Avandamet* in 190 poorly-controlled drug-naïve subjects with type 2 diabetes.<sup>(8,10)</sup> Subjects that did not meet eligibility criteria for enrollment in Study 007 due to HbA1c >11% or FPG > 270mg/dL were enrolled provided they met all other inclusion and exclusion criteria. *Avandamet* treatment was initiated with a total daily dose of 4 mg/1000mg. As tolerated, the dose was increased to 6 mg/1500mg at Week 4 and to the maximum dose of 8 mg/2000mg at Week 8.<sup>(81)</sup> Subjects who did not show adequate glycemic lowering were withdrawn for insufficient therapeutic effect if they had been on *Avandamet* 8 mg/2000 mg for at least 4 weeks and the FPG was >240 mg/dL.

Included among the secondary endpoints of Study 007 was an assessment of the effects of study treatment on serum lipid parameters. At baseline, approximately one-third of subjects were receiving statin therapy and were equally distributed across treatment groups.<sup>(9)</sup> Please refer to the table below for the effects of study treatment on total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides (TG).

**Table 24. Percent Change from Baseline to Week 32 in Lipid Parameters\* (Safety Population)<sup>(8,9)</sup>**

	<i>Avandamet</i> n† = 132	Rosiglitazone n† = 128	Metformin n† = 117
Total Cholesterol (mg/dL)			
Baseline (mean)	200.4	198.4	201.6
% Change from baseline (mean)	-2.2	5.3	-9.0
LDL Cholesterol (mg/dL)			
Baseline (mean)	113.8	114.6	116.0
% Change from baseline (mean)	-0.2	4.5	-10.7
HDL Cholesterol (mg/dL)			
Baseline (mean)	42.6	42.8	42.9
% Change from baseline (mean)	5.8	3.1	0.0
Triglycerides (mg/dL)			
Baseline (mean)	180.3	166.6	175.7
% Change from baseline (mean)	-18.7	-4.8	-15.4
* Data presented as geometric means throughout table; † Number of subjects with a baseline and end of treatment value			
HDL = High-density lipoprotein; LDL = Low-density lipoprotein			

After 32 weeks of treatment, *Avandamet* increased HDL by 5.8% compared with a 3.1% increase with rosiglitazone and no change in the metformin treatment group. TG decreased by 18.7%, 15.4% and 4.8% in the *Avandamet*, metformin and rosiglitazone treatment groups, respectively. TC and LDL did not increase in subjects treated with *Avandamet*. Metformin significantly lowered TC ( $P = 0.0019$ ) and LDL ( $P = 0.0161$ ) compared with *Avandamet*.<sup>(9,80)</sup>

## 9. OUTCOME AND ECONOMIC EVALUATION

### Background

An estimated 20.8 million Americans are affected by diabetes. <sup>(21)</sup> Type 2 diabetes accounts for 90 to 95% of all diagnosed diabetes cases and affects more than 18 million people in the United States. <sup>(109)</sup> The American Diabetes Association (ADA) has estimated the total cost (direct and indirect) attributable to diabetes to be \$132 billion in 2002.<sup>(21)</sup> Over two-thirds of these costs were direct medical costs such as those due to hospitalization, outpatient visits, and the rest were indirect costs such as those due to lost productivity.

Health problems from diabetes are a serious issue in the U.S. <sup>(109)</sup> The State of Diabetes Complications in America report shows that 3 out of 5 people with type 2 diabetes has at least one of the serious health problems connected to the disease such as, heart disease, stroke, eye damage, kidney disease, and foot problems that can lead to amputation. Estimated annual healthcare costs for a person with diabetes and its related complications are about three times that of the average American without diagnosed diabetes.

Large-scale studies have demonstrated that tight glycemic control greatly reduces the frequency and severity of long-term diabetes-related complications. In the 10-year United Kingdom Prospective Diabetes Study (UKPDS), intensive glycemic control resulted in HbA1c levels that were significantly lower than in patients on conventional therapy.<sup>(110)</sup> According to the UKPDS 35 Study, every 1% decrease in HbA1c resulted in a 21% decrease in risk of any diabetes-related end point. <sup>(111)</sup> The primary goal of diabetes therapy should be to prevent the occurrence of diabetic complications by enhanced glycemic control and treatment of insulin resistance.

### Treatment Adherence with *Avandia*

A retrospective cohort study was conducted using patient data from the North Carolina Medicaid program database queried from July 1, 2001 to June 30, 2002.<sup>(112)</sup> Patients were followed up for complete healthcare service utilization (hospitalizations, emergency department visits, outpatient physician visits, utilization of antidiabetic medication) and costs. Measures of adherence (medication possession ratio) and persistence (index of treatment persistence) were used to assess utilization of antidiabetic medication. Total annual healthcare costs were compared for Medicaid recipients newly started on thiazolidinediones (TZDs) vs. other oral antidiabetic agents. When healthcare costs were compared for Medicaid recipients newly started on TZDs vs. other oral antidiabetic agents, cost savings were realized for the TZD cohort as early as 2 years following therapy initiation (\$9,458 vs. \$10,629,  $P < 0.05$ ). Patients starting TZDs had 16% lower total annual healthcare costs compared to patients starting other oral antidiabetics ( $P < 0.01$ ). The persistence and adherence rates for the TZD group were statistically significantly higher than the oral antidiabetics group at nearly 9% and 13%, respectively ( $P < 0.01$ ). The subanalysis comparing the two TZDs, *Avandia* and pioglitazone, showed no significant differences between the two TZD groups in total annual healthcare costs, treatment adherence, or persistence rates.

An extended analysis was conducted to examine the original cohort of patients for an additional 18 months (up to December 2004) of observational follow-up.<sup>(113)</sup> Average healthcare costs for patients on a TZD were less compared to the metformin and other sulfonylurea groups ( $P < 0.05$ ). Overall, TZD's were associated with improved adherence but not persistence.

A separate analysis utilizing the same Medicaid database compared healthcare utilization and costs associated with initiation of treatment with either *Avandia* or pioglitazone in type 2 diabetes patients.<sup>(114)</sup> *Avandia* monotherapy was associated with a 12.2% decrease in the mean number of hospitalizations, a 10.4% decrease in mean number of emergency department visits, and 7.3% decrease in total healthcare costs compared with the pioglitazone monotherapy group ( $P < 0.05$  for all comparisons).

### **Treatment Adherence with *Avandamet***

Changes in medication adherence rates associated with switching from metformin or rosiglitazone monotherapy, or metformin plus rosiglitazone dual therapy, to *Avandamet* Fixed Dose Combination Therapy (FDCT) were assessed using a health plan claims database.<sup>(20)</sup> Medication possession ratio (MRP) was used to measure medication adherence. Patients switching from either monotherapy to FDCT had significantly less reduction in the mean MRP change than those switching from either monotherapy to dual therapy (-4.6% vs. -12.4%,  $P < 0.001$ ). Further, the analysis revealed that patients switching from dual therapy to FDCT also exhibited a significant improvement in the mean MRP change compared to those on continuous dual therapy (3.5% vs. -1.3%,  $P < 0.005$ ). Overall, the results of this retrospective analysis demonstrate that a statistically significant improvement in medication adherence rate results from the utilization of *Avandamet* FDCT when compared to rosiglitazone plus metformin dual therapy.

## **10. ECONOMIC MODEL**

### ***Avandamet*: Economic Model**

#### **Purpose**

The purpose of the budget impact model is to determine the impact of changes in market share distribution for *Avandamet*, Glucovance® (glyburide and metformin HCl, Bristol-Myers Squibb Company), Metaglip® (glipizide and metformin HCl, Bristol-Myers Squibb Company), Actos® (pioglitazone, Takeda Pharmaceuticals America, Inc.) plus metformin, and *Avandia*® (rosiglitazone) plus metformin on a State Medicaid budget. This information will help decision makers understand the impact of changes in utilization of these oral antidiabetic drugs in a population of patients with type 2 diabetes who are not controlled with metformin monotherapy. The overall objective of this model is to estimate the economic impact of the increase of *Avandamet* use compared to Glucovance®, Metaglip®, pioglitazone plus metformin, and rosiglitazone plus metformin under a pre-defined utilization scenario in a Medicaid population.

#### **Methods**

GlaxoSmithKline developed the model using Microsoft Excel. The model estimates the number of patients in a population who have type 2 diabetes and are not controlled with metformin monotherapy. This model calculates drug costs for *Avandamet*, Glucovance®, Metaglip®, pioglitazone plus metformin, and rosiglitazone plus metformin based on wholesale acquisition cost (WAC), daily average consumption (DACON) estimates, and the distribution of the population taking each dose combination. WAC is the listed price to wholesalers and warehousing chains, not including prompt pays, stocking or distribution allowances, or other discounts, rebates or charge backs. DACON was defined as the number of tablets consumed by each patient per day.

The following parameters are used in the model:

1. The total number of people in the Medicaid population (n = 500,000).
2. The prevalence of diagnosed type 1 and type 2 diabetes (the default is 6%).
3. The prevalence for type 2 diabetes (the default is 90%).
4. The percentage of type 2 diabetes patients who are not controlled with metformin monotherapy (the default is 10%).
5. The pricing information for each drug (the default is WAC, Wolters-Kluwer, August 2006).
6. The distribution of patients according to the dosage form of each drug (the default is based on DACON estimates from NDC Health, March 2006).
7. The percentage of patients taking each drug before and after changes in the market distribution (Table 25).

Model results are automatically generated upon entry of the information in steps 1-7.

**Table 25. Percentage of Patients on Each Product (hypothetical distribution)**

	Beginning Market Share	Ending Market Share
<i>Avandamet</i>	14%	44%
<b>Glucovance®</b>	50%	47%
<b>Metaglip®</b>	4%	3%
<b>Pioglitazone + metformin</b>	16%	3%
<b>Rosiglitazone + metformin</b>	16%	3%

Table 26 below illustrates the average cost per person per day of *Avandamet*, Glucovance®, Metaglip®, pioglitazone plus metformin, and rosiglitazone plus metformin. For these particular combinations, the following assumptions were made:

- Price per 1000 mg tablet of generic metformin: \$0.64
- Wholesale Acquisition Cost of *Avandamet*:
- 2 mg/500 mg: \$1.70/tablet
- 4 mg/500 mg: \$2.88/tablet
- 2 mg/1000 mg: \$1.70/tablet
- 4 mg/1000 mg: \$2.88/tablet
- Wholesale Acquisition Cost of Glucovance®:
- 1.25 mg/250 mg: \$0.82/tablet
- 2.5 mg/500 mg: \$0.98/tablet
- 5 mg/500 mg: \$0.98/tablet
- Wholesale Acquisition Cost of Metaglip®:
- 2.5 mg/250 mg: \$0.74/tablet
- 2.5 mg/500 mg: \$0.88/tablet
- 5 mg/500 mg: \$0.88/tablet
- Wholesale Acquisition Cost of pioglitazone:
- 15 mg: \$3.25/tablet
- 30 mg: \$5.21/tablet
- 45 mg: \$5.65/tablet
- Wholesale Acquisition Cost of rosiglitazone:
- 2 mg: \$1.95/tablet

- 4 mg: \$2.89/tablet
- 8 mg: \$5.25/tablet
- DACON for pioglitazone plus metformin and rosiglitazone plus metformin: 1.0 at all dose combinations

**Table 26. Average Cost Per Day of Therapies of Interest**

	DACON	\$Cost/tablet	Average \$ Cost/person/day
<b><i>Avandamet</i></b>			
2 mg/500 mg	2.1	\$1.70	\$3.57
4 mg/500 mg	1.8	\$2.88	\$5.18
2 mg/1000 mg	1.9	\$1.70	\$3.23
4 mg/1000 mg	1.9	\$2.88	\$5.47
<b>Glucovance®</b>			
1.25 mg/250 mg	2	\$0.82	\$1.64
2.5 mg/500 mg	2.5	\$0.98	\$2.45
5 mg/500 mg	3	\$0.98	\$2.94
<b>Metaglip®</b>			
2.5 mg/250 mg	1.9	\$0.74	\$1.41
2.5 mg/500 mg	2.4	\$0.88	\$2.11
5 mg/500 mg	2.6	\$0.88	\$2.29
<b>Pioglitazone + metformin</b>			
15 mg + 1000 mg	1	\$3.89	\$3.89
30 mg + 1000 mg	1	\$5.85	\$5.85
15 mg + 2000 mg	1	\$4.53	\$4.53
30 mg + 2000 mg	1	\$6.49	\$6.49
45 mg + 2000 mg	1	\$6.93	\$6.93
<b>Rosiglitazone + metformin</b>			
2 mg + 1000 mg	1	\$2.59	\$2.59
4 mg + 1000 mg	1	\$3.53	\$3.53
8 mg + 1000 mg	1	\$5.89	\$5.89
4 mg + 2000 mg	1	\$4.17	\$4.17
8 mg + 2000 mg	1	\$6.53	\$6.53

**Key Assumptions**

The hypothetical scenario presented below includes assumptions that were developed from product information and published literature. First, it was assumed that there were 500,000 Medicaid recipients in the State. The prevalence of diabetes among them was assumed to be 6%. The vast majority (90%) were assumed to have type 2 diabetes, of whom 10% were assumed to be inadequately controlled with metformin monotherapy. This scenario is hypothetical, and is not intended to approximate reality.

**Model Results**

This hypothetical scenario assumes that *Avandamet* receives approximately 80% of pioglitazone plus metformin combination therapy and rosiglitazone plus metformin combination therapy market shares, and Glucovance® and Metaglip® market shares are reduced from 50% to 47% and 4% to 3%, respectively.

Table 27 summarizes the economic impact given the assumption of the model with a cohort of 2,700 patients with type 2 diabetes who are not controlled with metformin monotherapy. Differences in costs were estimated for *Avandamet*, Glucovance®, Metaglip®, pioglitazone plus metformin, and rosiglitazone plus metformin and are summarized below.

**Table 27. Patients Not Controlled with Metformin Monotherapy - Estimated Total Economic Impact**

	Beginning Market Share	Beginning Cost	Ending Market Share	Ending Cost	Cost Savings
<b><i>Avandamet</i></b>	14%	\$567,084	44%	\$1,782,266	
<b>Glucovance®</b>	50%	\$1,295,192	47%	\$1,217,480	
<b>Metaglip®</b>	4%	\$84,868	3%	\$63,651	

<b>Pioglitazone + metformin</b>	16%	\$951,788	3%	\$178,460	
<b>Rosiglitazone + metformin</b>	16%	\$830,091	3%	\$155,642	
<b>Totals</b>	100%	<i>\$3,729,023</i>	100%	<i>\$3,397,499</i>	<b>\$331,524</b>
					<b>8.89%</b>

Based on the default scenario, the shift in *Avandamet* market share will save over 8.5% in drug costs in the environment where patients are prescribed Glucovance®, Metaglip®, pioglitazone plus metformin combination therapy, or rosiglitazone plus metformin combination therapy. Using WAC as a default, the use of *Avandamet* compared to the other combination therapies may result in a significant decrease in pharmacy expenditures. This represents an overall reduction in Medicaid pharmacy costs of \$331,524 or 8.89%.

#### Discussion of Model Results

Increase in use of *Avandamet* provides an opportunity to reduce Medicaid pharmacy costs and provide glycemic control to patients in a convenient dose. While this model has shown reductions in overall pharmacy costs with the increase of *Avandamet* use, it does not account for the potential improvement in compliance with a fixed-dose combination product over combination therapy as separate tablets, nor does it account for the expected low number of episodes of hypoglycemia with *Avandamet*. These are two potential benefits of *Avandamet* and may lead to overall reduction in utilization of medical services among Medicaid recipients due to potential improvements in glycemic control and side effects.

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